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14. ABSTRACT The overall objectives of this cooperative agreement are to conduct research in pursuit of identifying the physiologic mechanisms responsible for the symptoms of pain, fatigue, and memory difficulties commonly seen in patients with Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses, etc.); to identify the risk factors for developing these syndromes as well as programs aimed at both preventing these illnesses and treating established cases. These objectives will be achieved through multiple research studies using innovative, technologically advanced (e.g., functional MRI and telemedicine) methodologies in a multidisciplinary environment. Various studies will be conducted to explore all aspects of pain processing, the effects of exercise deprivation and sleep reduction on symptomatology, the ability of exercise and/or cognitive behavioral therapies to alter patients' locus of control for pain, the neurobiological mechanism(s) of acupuncture on analgesia, the presence of hypersensitivity to auditory stimuli, and the effectiveness of cognitive behavioral therapy delivered via telemedicine and the internet. These studies will be conducted on well-characterized cohorts of CMI subjects and healthy controls taken from our burgeoning subject registry. Research continues at the University of Michigan, Ann Arbor, MI and Avera Research Institute, Sioux Falls, SD.					
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Mechanisms in Chronic Multisymptom Illnesses
Annual Report 2007-2008
PI: DJ. Clauw

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Mechanisms in Chronic Multisymptom Illnesses

PI: Daniel J. Clauw, MD

Annual Report 2007-2008

DAMD 17-00-2-0018

1. INTRODUCTION

Researchers in the Chronic Pain and Fatigue Research Center (CPFRC) and collaborators within the University of Michigan and at the Avera Research Institute in Sioux Falls, SD are conducting research on human subjects in pursuit of identifying mechanisms in Chronic Multisymptom Illnesses (CMI), such as fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses etc. The research objectives include identifying:

- the physiologic mechanisms responsible for three prominent symptoms of CMI: pain; fatigue; and memory difficulties
- the risk factors for developing these syndromes; and
- programs aimed at both prevention of these illnesses and treatment of established cases.

These objectives will be achieved in a multidisciplinary environment and will employ the use of innovative, technologically advanced methodologies, including functional MRI (fMRI), Positron Emission Tomography (PET), proton Magnetic Resonance Spectroscopy (H-MRS), assessments of sensory processing, autonomic, and hypothalamic pituitary adrenal functions, multi-dimensional patient characterization, and the use of the internet (i.e. telehealth) to disseminate educational interventions.

2. BODY

To achieve the program objectives, a number of specific aims have been identified:

- develop a registry of diagnosed CMI research subjects and healthy controls to be accessed for ongoing study recruitment efforts;
- extensively study the psychological and neurobiological measures of pain processing in this spectrum of illnesses;
- determine whether an established non-pharmacological intervention, such as Cognitive Behavioral Therapy (CBT) can be translated into an online platform and effectively administered using an internet-based educational format;
- explore both the physiologic and treatment effects of exercise and sleep on these illnesses;
- determine if individuals with fibromyalgia suffer from an overall heightened sensitivity to physical stimuli (in this case auditory);
- examine neurocortical activation correlates of pain processing when individuals with FM enhance the internality of their locus of pain control either through relaxation therapy or exercise training;
- study the neurobiological mechanism(s) of acupuncture analgesia from a Western perspective on patients with fibromyalgia.

The specific aims of this program are being addressed through several individual research studies, each of which is described in further detail below. To maximize study participation and

minimize unnecessary redundancies in subject recruitment and screening, all interested study candidates who visit the CPFRC complete an extensive, centralized registry protocol. This occurs prior to participating in a specific study. Patients receive a brief phone screen, if eligible, are invited to complete the Registry battery, and are then invited to take part in any study, or studies, for which they qualify. Informed consent is obtained from each participant before any Registry data is collected. Separate informed consent processes are completed for each subsequent specific study.

All but one of the studies has been performed at the University of Michigan. The study examining effectiveness of internet-based CBT was conducted at the Avera Research Institute, Sioux Falls, SD.

University of Michigan, Ann Arbor, MI:

1. Subject Registry for Interdisciplinary Studies of Chronic Multisymptom Illnesses at the University of Michigan

Study Overview. This protocol involves the development of a centralized Subject Registry that:

- (a) acts as a repository of interested study volunteers;
- (b) provides a general first-level screening of participants; and
- (c) matches volunteers to current or future studies for which they may be able to undergo a non-redundant and briefer study-specific screening.

Demographic information and diagnostic information is collected on each candidate regarding their general physical and psychiatric (Axis I and II) status, their specific CMI symptomatology, and the influence/interplay of CMI symptoms on their life. Under this protocol, blood samples are collected and stored for future genetic studies of risk factors for developing these pain conditions. Future genetic studies will be funded by other mechanisms/sources.

Progress 2007-2008. Since September 2007, 74 new subjects have been added to the CPFRC Subject Registry, bringing the total to 585. The registry is not a hypothesis driven protocol but rather a resource for characterizing individuals for more efficient recruitment into other hypothesis driven protocols within our research center.

The following table summarizes the composition of the Subject Registry to date:

Table 1. Composition of Subject Registry

	Healthy Controls	CMI	Other
Female	124	246	115
Male	20	18	62
Total	144	264	177
<i>Average age</i>	<i>39 years</i>	<i>48 years</i>	<i>35 years</i>

Current as of December 2008

The year 2007-2008 represented the first year of our no-cost extension. Under the no-cost extension we continue to schedule and recruit individuals into the Registry as this represents a critical resource for conducting clinical research within our Center.

2. The Effect of Exercise and Sleep Deprivation on the Development of Chronic Multisymptom Illnesses Symptoms

Study Overview. The broad aim of this study is to evaluate the individual and synergistic effects of two different lifestyle disruptions: exercise and sleep deprivation. Our underlying hypothesis is that some individuals are prone to CMI symptom development while others are not. It is this group of susceptible individuals, in this case, runners, in whom we are interested. We hypothesize that a subset of test group will present with physiological markers of an attenuated physiological stress response that acts as a diathesis for the potential development of CMI, like fibromyalgia and Gulf War Illness.

Eligible study participants included individuals between the ages of 18-40 years; who regularly ran 5 or more days per week; and who routinely slept between 7-9 hours per night. Participants were followed for a total of 24 days, including 7-days of baseline, 10-days of a restriction period, and 7-days of follow-up. Prior to restriction we evaluated autonomic nervous function, the hypothalamic pituitary adrenal axis, and symptom report. During the restriction phase participants kept daily records of pain and fatigue symptoms and completed a more detailed series of symptom questionnaires approximately 2/3 of the way through the 10-day period. During the follow-up phase, we repeated the baseline testing battery and had participants complete a final series of symptom questionnaires on their final day in the study.

Status/Results to date. Recruitment for this study ended in 2006 with a total of 112 individuals accepted into the protocol, including 56 females and 56 males. Of these individuals, 95 completed participation and 17 withdrew prior to completing the study. The most common reasons for withdrawal were time constraints and unrelated illness/injury. Only 1 participant withdrew because of his group assignment (exercise deprivation). Our primary recruitment strategies were word-of-mouth and the University of Michigan's centralized clinical research site, *Engage*.

At first look, it appears that among healthy, regularly exercising and sleeping individuals, disruption of their normal routine was associated with increased somatic symptoms. From this sample we can further suggest that a segment of healthy, symptom-free individuals possess certain baseline neurophysiological characteristics that predict subsequent symptom development.

Preliminary analysis was presented in the 2006-2007 report. Two abstracts reflecting preliminary results were presented at November 2007 conference of the American College of Rheumatology and were included as appendices in the 2007 Annual Report. Data analysis continues and presentation of results via scientific conference proceedings, publications or future research pursuits is anticipated in 2009.

3. Mechanisms of Acupuncture Analgesia

Study Overview. In an innovative mix of modern technology and alternative therapies, we are using acupuncture as a potential placebo, along with fMRI, PET, and H-MRS, to determine specific neurological mechanisms of placebo analgesia. Within this study we aim to better define opioidergic mechanisms that underlie pain and the placebo effect. Preliminary data, presented in the 2006-2007 report, suggest that patients with fibromyalgia have evidence of increased occupancy of μ -opioid receptors at baseline. This suggests that their endogenous opioidergic systems are maximally activated and in spite of this they are still experiencing severe

pain. If these findings are confirmed it may help explain why opioid drugs are not clinically effective in chronic pain conditions such as fibromyalgia.

Status/Results to date. Recruitment for this study has closed with a total of 45 fibromyalgia patients and 15 healthy controls enrolled (the healthy control group was added as a recent amendment to the protocol). All but one fibromyalgia patient have completed the study.

The major findings from this study are that:

1. Fibromyalgia patients have reduced opioid receptor binding ability in brain regions known to modulate pain, and
2. Fibromyalgia patients who show longitudinal reductions in insular glutamate show reductions in both clinical and experimental pain.

We have also reported in abstract to national meetings that glutamate levels within the anterior insula seem to be associated with stress and anxiety whereas glutamate in the posterior insula seems to be associated with pressure pain intensity. Furthermore, fibromyalgia patients have elevated levels of glutamate within the posterior insula as compared to pain free controls.

Overall, these findings suggest that fibromyalgia patients have altered excitatory and inhibitory neural activity in brain regions known to process pain. Please refer to appended abstracts for further details.

4. Pain Mechanisms in Chronic Multisymptom Illnesses

Study Overview. This study aims to assess sensory processing abnormalities in CMI. Methods include various psychophysical paradigms such as ascending stimuli, random stimuli, pressure, temperature, etc., as well as fMRI to extensively examine the activity of endogenous analgesic systems. This includes descending antinociceptive activity (i.e. diffuse noxious inhibitory controls [DNIC]); aberrant afferent sensory stimuli processing; and, abnormal cortical and sub-cortical central nervous system function in groups with various CMI. This study also examines the extent to which cognitive and/or psychological processes affect pain processing in both normal individuals and individuals with these illnesses. Finally, this study will explore whether individuals with chronic pain may have a global disturbance in sensory processing by concurrently measuring auditory threshold and pain thresholds.

Status/Results to date. Recruitment for this particular study has ended with a total of 58 participants enrolled. We continue to examine descending antinociceptive (DNIC) activity, as well as overall sensory abnormalities, in individuals with chronic pain states and in normal healthy individuals. Data analysis continues and presentation of results via scientific conference proceedings, publications or future research pursuits is anticipated in 2009.

5. Locus of Pain Control: Neural Substrates and Modifiability

Study Overview. This protocol is an NIAMS/NIH funded R01 (AR050044) that has a small cost sharing component with this DOD cooperative agreement (DAMD 17-00-2-0018) that supports some of the costs of neuroimaging.

In preliminary studies, we demonstrated that internal locus of pain control (i.e., the belief that personal effort influences pain) had a strong relationship with neurocortical activation in specific brain regions associated with pain processing and modulation (i.e. using fMRI). Individuals with greater internal locus of control reported lower pain ratings.

In the current study, we sought to extend these findings by using two non-pharmacological methods of increasing internal pain locus of control in individuals with

fibromyalgia. Patients with fibromyalgia were randomized to receive either (a) training in relaxation, (b) training in aerobic fitness (exercise), or (c) standard care. A healthy control group was also studied. Neuroimaging was conducted at baseline and again 8 weeks later at post treatment. We hypothesized that individuals who improved internal locus of control by any means would demonstrate lower pain report and greater neurocortical activation of pain modulatory regions at post-treatment as evidenced by fMRI.

Progress 2007-2008. Recruitment for this study began in August 2005 and finished in early 2008. In total 123 patients enrolled into the study with 97 subjects completing both assessments. The following table summarizes the composition of the Locus of Control Study:

Table 2. Composition of Locus of Control Study

	FM: relaxation	FM: exercise	FM: std care	Healthy Controls
Females	25	24	24	24
<i>Average age</i>	<i>43 years</i>	<i>48 years</i>	<i>46 years</i>	<i>41 years</i>

The study conduct phase of this protocol required more time than originally planned (i.e. recruit and data collection). Thus, both funding sources (i.e. DOD and the NIH R01) went into no-cost extension during the past year. This resulted in a substantial loss of study staff and the speed by which data could be prepared for analysis. The leading neuroimaging faculty member also changed institutions requiring us to train new junior faculty. Remaining funds at reduced effort were allocated to the processing/analysis of neuroimaging data and the management of clinical data from the study.

Despite challenges in staffing this project in the past year, the data that has been collected represents a valuable and unique dataset that will provide a fertile resource for many manuscripts over the next several years. Thus in the past year, most effort was devoted to processing the clinical, neuroimaging, real-time pain ratings (EMA), evoked pain ratings, lab-based cortisol, and questionnaire data for consolidation into a large dataset for subsequent analysis. Analytic work to date on this dataset is being segregated into five initiatives: (a) confirmation of neurocortical correlates for internal locus of control's role in pain processing and pain modulation, (b) identifying which non-pharmacological intervention best improved internal locus of control, (c) identifying neurocortical correlates to changes in clinical pain over time, and (d) analysis of default mode functional connectivity (i.e. which areas of the brain communicate with one another at rest in patients with chronic pain) at two points in time with and without an intervention.

Confirmation of neurocortical correlates of LOC in pain processing and modulation

Due to a change in faculty expertise in these analyses, Dr. Jon-Kar Zubieta and Richard Harris joined our analytic team looking at these questions. These experts have requested that the data be processed somewhat differently than was done originally. Thus our dataset is being migrated into a new analytic platform (SPM from Medx). Apriori volumes of interest have also been identified; but have required additional time and effort to draw for each subject and process. It is anticipated that the additional preliminary work being done in the current year will yield manuscripts in 2009.

Identifying non-pharmacological interventions that best improve internal locus of control.

This dataset is beginning to yield results. Currently a manuscript is being prepared showing that our exercise intervention produced significantly greater improvement in internal locus of control than did the other two arms of the study.

Identifying neurocortical correlates in clinical pain over time.

Our total sample of individuals with fibromyalgia was divided into those who (a) reported an improvement in pain from baseline to 8 weeks post treatment and those who (b) reported a worsening of clinical pain over the same time period. A third group, reported no change over time. Using fMRI at baseline and at post treatment permitted an analysis of differential neurocortical activation in pain processing and pain modulation regions of those who got worse, stayed the same, or improved in clinical pain.

Results suggests that even over fairly long periods of time, fMRI of pain processing is relatively stable in fibromyalgia patients for whom there was no significant change in clinical symptoms. Changes in neurocortical activation proceeded in a predictable manner consistent with the experience of clinical pain in those who worsened or improved. The attached abstracts provide details regarding specific brain regions involved.

These data are being expanded upon and will be the topic of one of the first manuscripts examining longitudinal fMRI data in fibromyalgia.

Analysis of default mode functional connectivity in Fibromyalgia

Dr. Robert Welsh was joined by Dr. Scott Peltier to explore the default mode network in individuals with fibromyalgia. To date, two technical abstracts have emerged based upon these data. The first abstract demonstrates the ability for a novel data-driven technique to divide a key pain-processing brain region (the insular cortex) into functionally distinct areas. The second abstract demonstrates that fibromyalgia patients differ in their resting-state connectivity to two of these functionally distinct areas within the insula cortex, compared to healthy controls.

Analysis of voxel-based morphometry in Fibromyalgia

Dr. Hsu and Dr. Welsh also explored regional gray-matter volume in both fibromyalgia patients and healthy controls, using a new method known as voxel-based morphometry. Fibromyalgia patients with clinical depression and/or anxiety showed less gray-matter volume in the left anterior insular cortex, compared to healthy controls. Furthermore, the gray-matter volume from this region correlated significantly with anxiety levels. The attached abstract is from a manuscript currently under review.

Partnership with Avera-McKenna Research Hospital, Sioux Falls, SD:

6. Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia

Study Overview. This non-pharmacologic treatment intervention was designed to translate a successful evidence-based intervention (i.e. CBT) into an online educational format applicable to rural individuals with FM, a form of CMI. The study developed intervention materials for delivery in paper, CD-media, and internet platforms. The electronic media was used in a randomized controlled trial with outcomes focused upon pain, fatigue and overall well-being. Two study arms were compared: (a) standard care, and (b) standard care plus the educational

media. This project was designed by the investigators at the University of Michigan and the Avera-McKenna Research Hospital along with its various rural satellite clinics serving as performance sites. Given that as many as 14% of active duty personnel experience chronic symptom-based conditions and that this spectrum of illness occurred much more frequently after the Gulf War and other deployments, this project could have enormous impact on how these service members receive healthcare.

The content of the multidisciplinary educational CD covers three main topic areas: overview of fibromyalgia including a discussion of causes and treatment advice; symptom management including medications and CBT skills such as exercise, sleep, relaxation, and pleasant activities; and lifestyle management such as goal setting, problem solving, pacing, reframing, and communication. The educational CD contains standardized video lectures, homework assignments to practice skills learned, and an interactive goal tracking feature. This CD is also available as a website, which contains a chat room accessible to study participants and a link to electronic self-report forms. Web access is restricted to study participants who have signed a consent form, obtained a study identification number, and created a password. Since this site is not accessible to the general public, several screen shots have been included in the appendices to give examples of content and appearance.

Progress 2007-2008. The randomized controlled trial began in August 2006 and ended in October 2007 with the last subject completing the 6 month endpoint in April of 2008.

Like the locus of control study described above, the study conduct phase of this protocol required more time than originally planned (i.e. recruit and data collection, completion of the 6 month follow-up assessment). Thus under no-cost extension, we emphasized getting all study participants through the final 6 month assessment. Data base cleaning, locking and dataset development for analysis has proceeded more slowly than desired due to the need to reduce staff effort under no-cost extension.

The following Table summarizes the composition of the Internet and Telehealth study:

Table 3. Composition of Internet and Telehealth Study

	Standard Care	Internet Education plus standard care
Males	4	3
Females	57	56
Total	61	59
<i>Average age</i>	<i>50 years</i>	<i>50 years</i>

To date, preliminary results indicate that patients in the intervention have experienced notable improvements in (a) clinical pain severity and (b) physical function compared to the standard care group. These patients have made good use of most of the intervention strategies, with emphasis on exercise training, relaxation techniques, pleasant activity scheduling, and goal setting skills. Patients in the intervention arm have actively used the CD and the internet and have reported receiving a high quality of healthcare from the intervention that has helped them to deal effectively with their fibromyalgia symptoms.

Further analysis of these data is planned and several manuscripts are being prepared. The first is a description of the intervention and a publication of the educational materials used in this intervention. The second will be the results of the randomized controlled trial later in 2009.

Other Notable Findings and Activities:

Impaired cognitive function, euphemistically labeled “fibro-fog,” is a common complaint in patients with fibromyalgia. In an analysis of working memory, we examined whether cognitive impairment could be the result of a faster rate of decay in fibromyalgia patients compared to healthy individuals. Our results indicate that difficulty managing competing or distracting information is the root of working memory problems in fibromyalgia, rather than a more rapid loss of information from working memory.

Results from our collective studies continue to suggest that CMI are more similar than they are different. Accumulating evidence indicates that these illnesses may be stemming from overall sensory dysfunction. In other words, patients who have long been known to share common symptoms of pain sensitivity, fatigue, and cognitive difficulties, may also share sensitivity to sound, may experience vertigo, and in general, may have greater sensitivity to a host of sensory experiences. We continue to examine these avenues through a host of pilot studies and studies funded via other mechanisms.

3. KEY RESEARCH ACCOMPLISHMENTS

- In the exercise/sleep deprivation study, we have observed that certain healthy individuals who experience a disruption of their normal exercise and/or sleep routines will develop autonomic nervous system activity and somatic symptoms similar to those that characterize CMI patients. Results from this particular study demonstrate that baseline abnormalities in autonomic and hypothalamic pituitary adrenal function predict the subsequent development of somatic symptoms. This represents a major paradigm shift in how these illnesses are viewed; where previously, we thought these abnormalities were causing the illness.
- Our functional imaging studies continue to show a number of objective abnormalities in pain processing in individuals with CMI. Perhaps the most remarkable finding is that it appears as though the endogenous opioid system is already maximally activated in patients with fibromyalgia because at baseline the μ -opioid receptor binding is diminished, and this value correlates strongly with clinical pain ratings. This important data is providing evidence for biomarkers and technology that may be beneficial in diagnosing, predicting, and ultimately, treating these illnesses.
- The treatment study underway looking at electronic media to help manage fibromyalgia represents the “cutting edge” of the pain field and could be useful in a number of clinical settings. Preliminary results are positive; indicating that patients who have used this technology as a therapeutic intervention have engaged in the activities provided and have reported good outcomes.

4. REPORTABLE OUTCOMES

In total, two journal articles have been published, a further two accepted for publication, and 15 abstracts presented since September 2007. The outcomes presented were all based on research conducted under the sponsorship of this program.

In addition, findings from these studies have been accepted for inclusion in two book chapters on Fibromyalgia and chronic pain syndromes.

Journal Articles

Michael C. Hsu, Richard E. Harris, Carlo Fernandes, Robert C Welsh, Pia M. Sundgren, Daniel J. Clauw, **Differences in Regional Gray-Matter Density between Fibromyalgia Patients and Controls: a Voxel-Based Morphometry Study.** Accepted for publication by the American Pain Society.

David A. Williams, Ph.D. Daniel J. Clauw, M.D. **What Fibromyalgia has Taught Us about Chronic Pain.** Accepted for inclusion in the Journal of Pain Volume 10

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Michael Hsu, Myria Petrou, Seong-Ho Kim, Samuel A. McLean, Richard H. Gracely, and Daniel J. Clauw (2008). **Dynamic Levels of Glutamate Within the Insula Are Associated with Improvements in Multiple Pain Domains in Fibromyalgia.** Arthritis and Rheumatism, 58, 3, pp903-907. (*See Appendix*)

Harris, R.E., Clauw, D.J., Scott, D.J., Mclean, S.A., Gracely, R.H., Zubieta, J. (2007). **Decreased Central μ -Opioid Receptor Availability in Fibromyalgia.** The Journal of Neuroscience. 27(37). pp 10000-10006. (*See Appendix*)

Abstract Presentations

Vitaly Napadow, Lauren Lacount, Kyungmo Park, Suzie As-Sanie, Daniel Clauw, Richard E Harris, **Intrinsic Resting Brain Networks Are Associated with Spontaneous Pain in Chronic Functional Pain Patients.** Submitted to the Human Brain Mapping conference, June 2009. (*See Appendix*)

S.J. Peltier, M.C Hsu, R.C. Welsh, R Bhavsar, R.E. Harris, D.J. Clauw, L. Symonds, L. Yang, D.A. Williams. **Data-driven parcellation of the insular cortex using resting-state fMRI.** Submitted to the Human Brain Mapping conference, June 2009. (*See Appendix*)

Poznanski, Ann, **Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM).** Presented at Medical Acupuncture in Integrative Care Meeting 2008, Singapore, August 2008.

Poznanski, Ann, Integrative Medicine: **When Main Stream Practice Embraces Alternative/Complementary Treatments, Fibromyalgia and Acupuncture: Clinical**

Research Update. Presented at the Michigan State Medical Society Annual Scientific Meeting, October 2008.

Poznanski, Ann A., Daniel J. Clauw, Pia Maly-Sundgren and Richard E. Harris. **Correlations between Insular Glutamate Levels and Pain-Evoked Neural Activity in Patients with Fibromyalgia.** Presented at the 11th International Conference on the Mechanisms and Treatment of Neuropathic Pain, Bermuda, November 2008. (*See Appendix*)

Poznanski, Ann, Michael Hsu, Richard H. Gracely, Daniel J. Clauw, and Richard E. Harris. **Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM).** Abstract accepted for the North American Research Conference on Complementary & Integrative Medicine, Minneapolis, Minnesota, May 2009.

Poznanski, A., Hsu, M., Gracely, RH., Clauw, DJ., and Harris, RE. **Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM).** Presented to the American Pain Society, 2008. (*See Appendix*)

Harris, RE. Sundgren, PC., Kirshenbaum, E., Xiang, Z., and Clauw, DJ. **Variation in Glutamate and Glutamine Levels within the Anterior Insula are Associated with Changes in Anxiety and Pain in Fibromyalgia (FM).** Presented to the American College of Rheumatology, 2008. (*See Appendix*)

Qiu, Y. Zubieta, J-K., Scott, D., Gracely, RH., Clauw, DJ. and Harris, RE. **Central μ -Opioid Receptor (MOR) Availability covaries with Mood State and Pain in Fibromyalgia (FM).** Presented to the American Pain Society 2008. (*See Appendix*)

Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., **Variation in Glutamate and Glutamine Levels within the Insula are associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM).** Presented at the International Association for the Study of Pain, 2008. (*See Appendix*)

Harris RE, Zubieta J-K, Scott DJ, Gracely RH, and Clauw DJ. **Differential Sustained Changes in μ -Opioid Receptor (MOR) availability following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM).** Presented to the American College of Rheumatology, 2007. (*See Appendix*)

Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., **Variation in Glutamate and Glutamine levels within the Insula are Associated with Improvements in Clinical and Experimental pain in Fibromyalgia (FM).** Presented to the American College of Rheumatology, 2007. (*See Appendix*)

Williams, DA, Patel, R., Skalski, L., Chriscinske, SJ, Rubens, M., Lapedis, J., Harris, RE, Gracely, RH, Clauw, DJ **Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time.** Arthritis and Rheumatism (abstract supplement), 56, 9, S91.

Patel, R., Williams, DA, Gracely, RH, Skalski, L., Chriscinske, SJ, Alesi, G., Clauw, DJ. **Functional MRI (fMRI) of Pain Processing is Stable Over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status.** Arthritis and Rheumatism (abstract supplement), 56, 9, S92.

Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, Williams DA. **No Difference in Gray Matter Volume between Fibromyalgia Patients and Age-Matched Healthy Subjects when Controlling for Depressive Disorder.**

Jennifer M. Glass, Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Richard H. Gracely, and Daniel J. Clauw. **Variation in Glutamate and Glutamine Levels within the Insula are Associated With Improvements in Working Memory in Fibromyalgia (FM).** *(See Appendix)*

Scott J. Peltier, Michael C. Hsu, Robert C. Welsh, Rupal Bhavsar, Laura, Yang, Richard E. Harris, Daniel J. Clauw, David A. Williams. **Data-driven parcellation of the insular cortex using resting-state fMRI.** *(See Appendix)*

Michael C. Hsu, Richard E. Harris, Carlo Fernandes, Robert C Welsh, Pia M. Sundgren, Daniel J. Clauw. **Differences in Regional Gray-Matter Density between Fibromyalgia Patients and Controls: a Voxel-Based Morphometry Study.** *(See Appendix)*

Book Chapters

David A. Williams. **Pain and Painful Syndromes (including RA and FM).** This is a manuscript for inclusion in J. Suls, K. Davidson, and R. Kaplan (Eds.), Handbook of Health Psychology, Guilford Press.

David A. Williams, Marissa L. Marshak. **Motivating Behavioral Change in Fibromyalgia.** This is a manuscript for inclusion in W. McCarberg and D.J. Clauw (Eds.), Fibromyalgia, Informa Health Care USA Press.

Links to Websites:

Chronic Pain and Fatigue Research Center: <http://www.med.umich.edu/painresearch/>

Website derived from materials produced under this grant, and licensed to Eli Lilly. www.fibroguide.com. This is a “non-branded” (no mention of Lilly’s drug) website available for anyone worldwide with fibromyalgia to use to improve symptoms, and is based on the content for the Avera study.

Gulf War Health information: <http://www.med.umich.edu/gulfwarhealth/>

5. CONCLUSION

Our research findings using innovative technologies like functional MRI (fMRI), Positron Emission Tomography (PET) and Magnetic Resonance Spectroscopy (H-MRS), continue to identify potential biomarkers for the diagnosis, prediction, and ultimately, the improved treatment of CMI.

We continue to employ web technology to deliver behavioral interventions to individuals in rural settings who would otherwise have difficulty receiving care. Preliminary results indicate that the individuals who have been assigned to receive an educationally-based behavioral intervention via web or CD have made good use of the skills provided and are reporting improvements in symptoms and overall quality of life. This technology could substantially improve healthcare delivery in a variety of settings, both rural and beyond.

Our research continues to observe symptom development in healthy individuals who experience a disruption to their normal exercise and/or sleep routines. This observation, coupled with baseline autonomic and hypothalamic pituitary adrenal function, provides valuable insight into the profile of an individual who appears to have a diathesis toward developing CMI. This could represent a major paradigm shift in how these illnesses are viewed because, previously, we thought these abnormalities were causing the illness.

Overall, research in CMI has grown substantially in the last few years extending our original findings in fMRI from several years ago to new frontiers in the understanding of pain today. Our research team continues to make substantial contributions to the growth of understanding and treatment of these illnesses through our dedication to research and clinical care.

6. REFERENCES

All references pertinent to this report are listed in section 4, Reportable Outcomes.

7. APPENDICES

The attached appendices contain information that supplements, clarifies or supports the text. Original copies of published journal articles have been included.

- a. Published Journal Articles
- b. Abstracts and/or Presentations
- c. Multi-media screenshots

Published Journal Articles

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Michael Hsu, Myria Petrou, Seong-Ho Kim, Samuel A. McLean, Richard H. Gracely, and Daniel J. Clauw (2008). Dynamic Levels of Glutamate Within the Insula Are Associated with Improvements in Multiple Pain Domains in Fibromyalgia. *Arthritis and Rheumatism*, 58, 3, pp903-907

Harris, R.E., Clauw, D.J., Scott, D.J., Mclean, S.A., Gracely, R.H., Zubieta, J. (2007). Decreased Central μ -Opioid Receptor Availability in Fibromyalgia. *The Journal of Neuroscience*. 27(37). pp 10000-10006.

Dynamic Levels of Glutamate Within the Insula Are Associated With Improvements in Multiple Pain Domains in Fibromyalgia

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Michael Hsu, Myria Petrou, Seong-Ho Kim, Samuel A. McLean, Richard H. Gracely, and Daniel J. Clauw

Objective. Fibromyalgia (FM) is a chronic widespread pain condition that is thought to arise from augmentation of central neural activity. Glutamate (Glu) is an excitatory neurotransmitter that functions in pain-processing pathways. This study was carried out to investigate the relationship between changing levels of Glu within the insula and changes in multiple pain domains in patients with FM.

Methods. Ten patients with FM underwent 2 sessions of proton magnetic resonance spectroscopy (H-MRS) and 2 sessions of functional magnetic resonance imaging (fMRI), each conducted before and after a nonpharmacologic intervention to reduce pain. During H-MRS, the anterior and posterior insular regions were examined separately using single-voxel spectroscopy. The levels of Glu and other metabolites were estimated relative to levels of creatine (Cr) (e.g., the Glu/Cr ratio). During fMRI, painful pressures were applied to the thumbnail to elicit neuronal activation.

Experimental pressure-evoked pain thresholds and clinical pain ratings (on the Short Form of the McGill Pain Questionnaire [SF-MPQ]) were also assessed prior to each imaging session.

Results. Both experimental pain ($P = 0.047$ versus pretreatment) and SF-MPQ-rated clinical pain ($P = 0.043$ versus pretreatment) were reduced following treatment. Changes from pre- to posttreatment in Glu/Cr were negatively correlated with changes in experimental pain thresholds ($r = -0.95$, $P < 0.001$) and positively correlated with changes in clinical pain ($r = 0.85$, $P = 0.002$). Changes in the fMRI-determined blood oxygenation level-dependent effect (a measure of neural activation) were positively correlated with changes in Glu/Cr within the contralateral insula ($r = 0.81$, $P = 0.002$).

Conclusion. Changes in Glu levels within the insula are associated with changes in multiple pain domains in patients with FM. Thus, H-MRS data may serve as a useful biomarker and surrogate end point for clinical trials of FM.

Fibromyalgia (FM) is a chronic widespread pain disorder that affects ~2–4% of individuals in industrialized countries (1). Although the underlying etiology of this condition is unknown, dysfunction within the central nervous system has been implicated. Results from functional magnetic resonance imaging (fMRI) (2,3), single-photon emission tomography (4), and positron emission tomography (5) support this hypothesis.

One structure that is consistently found to be associated with augmented evoked pain activity in FM is the insula (2,3). In addition to its function in speech, taste, and auditory systems, the insula is also intimately involved in somatosensory and visceral pain processing (6). It is strategically located in a bidirectional pathway between the secondary somatosensory cortex and the amygdala (6). This anatomic position may give the insula

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Dr. Harris has received consulting fees from Pfizer as part of an investigator-initiated study of acupuncture in fibromyalgia and has received speaking fees (less than \$10,000) from the University of North Carolina Pelvic Pain Conference. Dr. Clauw has received consulting fees, speaking fees, and/or honoraria (less than \$10,000) from Wyeth and (more than \$10,000 each) from Eli Lilly, Pfizer, Cypress Bioscience, and Forest Laboratories.

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a unique regulatory function within the “pain matrix.” Topographically, the posterior insula is thought to be involved in discriminative activities of sensory pain (7), whereas the anterior insula may play a greater role in processing the affective dimension of pain (8).

Glutamate (Glu) is a major excitatory neurotransmitter within the nervous system and is known to function in pain neuropathways. The binding of Glu to ionotropic receptors increases the sodium permeability of neuronal membranes and results in cell activation (i.e., membrane depolarization). Since elevated Glu levels have been reported in the cerebrospinal fluid of patients with FM (9), it is reasonable to suspect that this molecule may be responsible for the augmented pain transmission observed in FM (2,3).

We performed a longitudinal proton magnetic resonance spectroscopy (H-MRS) study to investigate the role of Glu within the insula of patients with FM. H-MRS is a noninvasive procedure that can be used to determine the relative concentration of specific brain metabolites *in vivo*. We focused our investigation on the changing levels of Glu following a nonpharmacologic treatment, within both the anterior and posterior insula of patients with FM. We hypothesized that changes in the levels of Glu should be positively correlated with changes in clinical pain. Conversely, changes in Glu levels should be negatively correlated with changes in pressure-evoked pain thresholds, since lower thresholds are indicative of greater pain sensitivity. In addition, we used FMRI in these same subjects to determine whether changes in Glu levels were related to changes in pain-related neural activity.

PATIENTS AND METHODS

Participants. As part of an ongoing study investigating the impact of acupuncture treatment in FM, 10 female patients (mean \pm SD age 48 ± 15 years) were examined in 2 sessions of H-MRS and 2 sessions of FMRI, with the sessions spaced 1 month apart (Figure 1). Participants were randomized to receive either 9 traditional acupuncture treatments or 9 non-skin-penetrating sham acupuncture treatments, administered between imaging sessions. All analyses described herein were carried out in a blinded manner with the treatment assignment masked, since we were not interested in the potential differential effects between treatment with acupuncture and sham treatment, but rather in whether changes in the levels of Glu correspond to changes in pain. All participants gave their written informed consent, and all study protocols were approved by the University of Michigan Institutional Review Board.

Participant inclusion and exclusion criteria have been reported previously (5). All participants met the American College of Rheumatology 1990 criteria for the diagnosis of FM

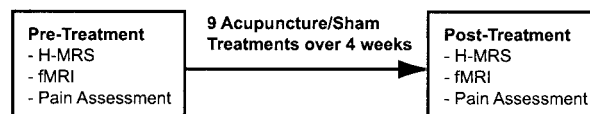


Figure 1. Experimental design. Patients with fibromyalgia underwent pretreatment assessments with both proton magnetic resonance spectroscopy (H-MRS) and functional magnetic resonance imaging (FMRI). During H-MRS testing, resting levels of glutamate were obtained in the insula. During FMRI, neural activations (i.e., BOLD [blood oxygenation level–dependent] effects) were elicited with painful pressure stimuli applied to the left thumbnail bed. Pretreatment assessments of clinical pain using the Short Form of the McGill Pain Questionnaire, and experimental pressure-evoked pain sensitivity thresholds were also obtained. Following the baseline assessment, participants received either 9 acupuncture treatments or 9 sham acupuncture treatments over 4 weeks. H-MRS, FMRI, and pain outcomes were then measured again, following the last treatment.

(10) and had a disease duration of at least 1 year. In addition, all patients reported experiencing pain for more than 50% of the days prior to the trial period.

H-MRS. All participants underwent conventional MR imaging of the brain on a General Electric 3.0T MR scanner (GE, Milwaukee, WI). Single-voxel spectroscopy (SVS) was performed using point-resolved spectroscopy, with a repetition time (TR) of 3,000 msec, echo time (TE) of 30 msec, 90° flip angle, number of excitations 8, field of view (FOV) 16 cm, and volume of interest (VOI) of $2 \times 2 \times 3$ cm. During each session, 2 separate SVS sequences were performed, once with the VOI placed in the right anterior insula and once in the right posterior insula (Figure 2A). The right insula was chosen because it is contralateral to the pressure-evoked pain stimulus applied during FMRI. Patients were at rest during both H-MRS sessions.

The raw data from each SVS sequence were subjected to manual postprocessing using H-MRS software (LCModel; Oakville, Ontario, Canada) (Figure 2B). Values for Glu, glutamine (Gln), and the combination of Glu and Gln (Glx) were calculated as ratios to an internal standard, the creatine (Cr) level (e.g., Glu/Cr). Similar calculations were done for other major metabolites, including *N*-acetylaspartate (NAA), choline (Cho) compounds, and myoinositol (MI). Although these other metabolites are not known to play a role in neuronal activity, they were measured to assess the relative specificity of Glu and Gln in our analyses.

Functional MRI. To assess the relationship between changes in Glu and changes in neural activity, all participants also underwent 2 FMRI sessions, once prior to treatment and once posttreatment. Functional MRI scans were acquired on the same 3.0T scanner as used for H-MRS. On each scanning day, subjects completed 2 FMRI runs, acquired with a spiral gradient-echo sequence (TR 2,500 msec, TE 30 msec, 90° flip angle, FOV 22 cm). Slices were 3-mm thick, with an in-plane resolution of 3.125×3.125 , acquired at 48 locations parallel to the anterior-posterior commissure plane. Preprocessing was performed using statistical parametric mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, London, UK) and included correction for slice-acquisition time to the middle slice, realignment to the first volume of each run to correct for

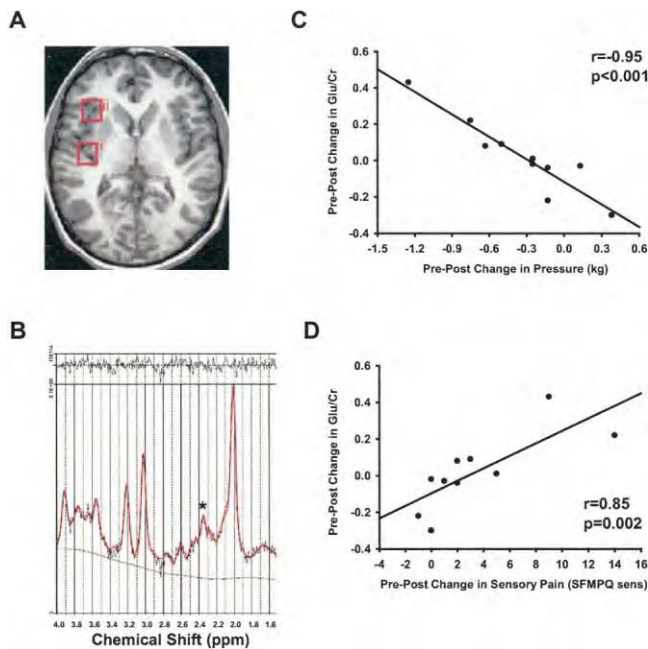


Figure 2. Association of changing levels of glutamate (Glu) with improvements in pain outcomes in patients with fibromyalgia (FM). **A**, Axial T1-weighted image showing single-voxel placement for both the posterior (i) and anterior (ii) right insula in proton magnetic resonance spectroscopy (H-MRS). **B**, Representative H-MRS spectrum from the posterior insula of a patient with FM, analyzed by fitting data with the LCModel, which uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (red trace); * = resonance from 2 Glu γ -proton resonances at 2.35 ppm. Values for Glu were calculated as a ratio to the creatine (Cr) internal standard (Glu/Cr). **C**, Negative correlation of pre- to post-treatment changes in Glu/Cr within the posterior insula with pre- to posttreatment changes in mildly painful pressure-evoked pain thresholds. **D**, Positive correlation of pre- to posttreatment changes in Glu/Cr within the posterior insula with pre- to posttreatment changes in clinical pain (assessed as the sensory pain score on the Short Form of the McGill Pain Questionnaire [SF-MPQ]).

intrascan movement, and smoothing with a Gaussian kernel of 8 mm full width at half maximum to compensate for small residual anatomic variations across subjects. Smoothed images were then band pass-filtered to eliminate low-frequency signals.

A general linear model was constructed with parameters corresponding to the type of pressure stimulus applied (either no touch or innocuous touch) in each block, with Gracely Box Scale (GBS) scores of 0.5 for low pain, 7.5 for mild pain, and 13.5 for moderate pain; modeling of each run was carried out separately. Blocks were 25 seconds in duration and presented according to a fixed pseudorandom paradigm in which every other block consisted of the “no touch” condition. To allow for comparison across individuals, 1 of the 3 painful pressure blocks was set to 2 kg/cm². Each stimulus block was convolved with a canonical hemodynamic response function. Parameter estimates of block-related activity were established

for each voxel, and contrast images were calculated by applying a linear contrast of the parameter estimates of the 2 kg/cm² pressure versus the “no touch” condition for each participant. The resulting statistical images obtained for each subject were then spatially normalized into International Consortium for Brain Mapping space by applying T1-weighted spoiled gradient echo transformation parameters to the SPM2 contrast image.

Differences in the blood oxygenation level-dependent (BOLD) effects (a measure of neural activation) from pretreatment to posttreatment were calculated (as a percentage) for the entire volume in each individual, and were assessed for correlations with Glu/Cr change scores (pretreatment to posttreatment) in the posterior insula. Our a priori hypothesis was that changes in BOLD activation within the insula would be correlated with changes in Glu/Cr values. Therefore, we used an uncorrected significance threshold of $P < 0.001$, with a minimum cluster size of 10 voxels for clusters identified within the insula. Individual BOLD activation responses were extracted using the Marsbar Region of Interest Toolbox (version 0.38; <http://marsbar.sourceforge.net>).

Clinical pain. Assessment of clinical pain was performed prior to each imaging session using ratings on the Short Form of the McGill Pain Questionnaire (SF-MPQ) (11). Our analysis focused on the sensory dimension of pain assessed by this questionnaire, since the magnitude of sensory pain was reduced with treatment.

Experimental pain. Pressure-evoked pain tenderness was assessed prior to each imaging session (12,13). Briefly, discrete pressure stimuli were applied to the subject's left thumbnail using a stimulation device that eliminates any direct examiner-subject interaction. Pain intensity ratings were recorded on a GBS questionnaire using a random presentation paradigm. During the testing, stimulus pressures were determined interactively; a computer program continuously adjusted the stimulus pressures at 3 levels to produce the same response distribution (i.e., GBS scores of 0.5, 7.5, and 13.5) in each subject. We assessed correlations of changes in metabolite levels with changes in the pressure-evoked pain thresholds at the mildly painful pressure level (GBS score of 7.5), since this threshold increased following treatment.

Statistical analysis. Ratios of the different metabolites to Cr, percent changes in BOLD activation, and pain ratings were analyzed using SPSS version 14 (SPSS, Chicago, IL). Due to our small sample size, we performed nonparametric Spearman's correlation tests to determine significant relationships between Glu/Cr and changes in pain outcomes. For these correlation analyses, a Bonferroni-corrected P value of less than 0.0042 (calculated as 0.05 divided by 12) was applied as the level of significance for correlations between changes in metabolite ratios (Glu/Cr, Gln/Cr, and Glx/Cr) and changes in pain domains (i.e., 2 brain regions [anterior and posterior insula], 2 pain domains [clinical and experimental], and 3 metabolites). A similar correction (corrected $P < 0.0042$) was performed for the analysis of baseline and posttreatment metabolite ratios within the posterior insula and changes in pain (i.e., 3 metabolites, 2 time points, and 2 pain domains). Nonparametric Wilcoxon's signed rank tests were performed to determine changes from pretreatment to posttreatment in clinical and experimental evoked pain.

RESULTS

Following acupuncture or sham treatments in this population of patients with FM, the pressure-evoked pain sensitivity after application of mildly painful pressures was significantly reduced (mean difference in experimental pain thresholds -0.34 kg [SD 0.46 kg]; $P = 0.047$). Moreover, clinical pain improved from pre- to posttreatment according to SF-MPQ ratings of the sensory dimension of pain (mean difference in clinical pain ratings 3.50 [SD 4.70]; $P = 0.043$).

Figure 2B depicts a representative spectrum obtained from the posterior insula of a patient prior to treatment. A significant negative correlation was detected between change scores for Glu/Cr in the posterior insula from pre- to posttreatment and changes in the pressures required to elicit mild pain from pre- to posttreatment ($r = -0.95$, $P < 0.001$) (Figure 2C). Similarly, a positive correlation was detected between changes in Glu/Cr in the posterior insula and changes in SF-MPQ (sensory) clinical pain ratings ($r = 0.85$, $P = 0.002$) (Figure 2D). Furthermore, higher levels of Glu/Cr in the posterior insula were also associated with greater reductions in clinical pain posttreatment ($r = 0.81$, $P = 0.004$).

No significant correlations were detected between change scores of any other metabolite ratios (i.e., NAA/Cr, Cho/Cr, or MI/Cr) in the posterior insula and changes in either clinical pain ratings or experimental evoked pain thresholds (all $P > 0.10$). In addition, no significant changes in Cr concentrations were detected within the posterior insula ($P = 0.98$).

Since there is debate as to whether H-MRS can accurately measure Glu separately from Gln within humans at 3T, we also assessed the combination of Glu and Gln as a ratio (i.e., Glx/Cr). Changes in Glx/Cr within the anterior insula ($r = -0.63$, $P = 0.049$) and posterior insula ($r = -0.62$, $P = 0.058$) were both negatively correlated with changes in pressure-evoked pain, albeit at the level of trend toward significance. Overall, these data are consistent with the idea that either insular Glu or insular Gln or both are associated with changes in multiple pain domains in FM.

Since Glu functions in pain neurotransmission, we next investigated whether pre- to posttreatment changes in Glu/Cr within the right posterior insula were associated with changes in the BOLD responses elicited by painful pressure applied to the thumbnail bed. Changes in Glu/Cr within the right posterior insula were positively correlated with changes in BOLD activation within the left posterior insula (T score 6.6, uncorrected

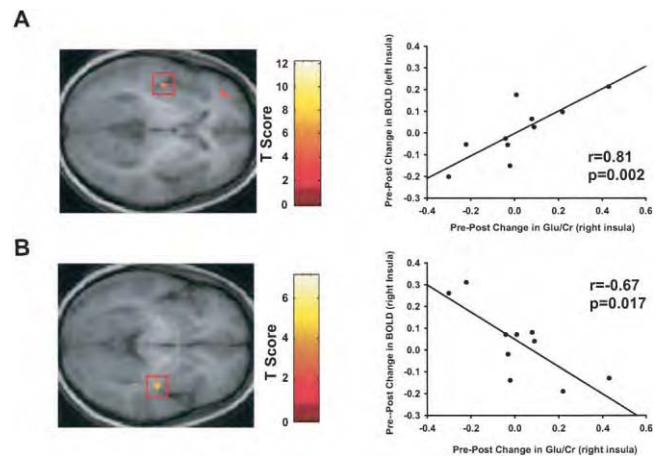


Figure 3. Association of dynamic levels of glutamate:creatine (Glu/Cr) within the posterior insula with changes in neural activity. **A**, Positive correlation of pre- to posttreatment changes in functional magnetic resonance imaging (fMRI)-determined blood oxygenation level-dependent (BOLD) activation within the left posterior insula with pre- to posttreatment changes in Glu/Cr within the right posterior insula (left). Scatterplot (right) depicts individual BOLD and Glu/Cr changes. **B**, Negative correlation of pre- to posttreatment changes in fMRI-determined BOLD activation within the right posterior insula with pre- to posttreatment changes in Glu/Cr within the right posterior insula (left). Scatterplot (right) depicts individual BOLD and Glu/Cr changes.

$P < 0.001$; Montreal Neurological Institute (MNI) coordinates $x = -42$, $y = -12$, $z = 0$) (Figure 3A). In contrast, a negative correlation, at the level of trend toward significance, was detected for changes in Glu/Cr and changes in BOLD activation in the right posterior insula (T score 4.1, uncorrected $P = 0.0018$; MNI coordinates $x = 38$, $y = -14$, $z = -6$) (Figure 3B).

DISCUSSION

These data are the first evidence of a correlation between changing levels of insular Glu and changes in pain in patients with FM. Since Glu is a major excitatory neurotransmitter involved in pain transmission, these observations are not unexpected. Our data are also consistent with findings from a recent H-MRS study in which increases in Glu/Cr within the anterior cingulate were observed in response to cold pain in healthy pain-free controls (14). However, the present data show primarily the converse of this relationship, namely, reductions in pain in association with lower Glu/Cr values.

Since detecting Glu-specific concentrations accurately at 3T in humans is difficult because of the

overlapping proton resonances between Gln and Glu, we also investigated the combinations of Glu/Cr and Gln/Cr (i.e., Glx/Cr), which may be less controversial (14). Similar to the above-described results, we found that pre- to posttreatment changes in Glx/Cr within the insula were negatively correlated with pre- to posttreatment changes in pressure-evoked pain thresholds. Since we did not detect a significant relationship between changes in any other major metabolites and improvements in pain outcomes, our findings are likely to be specific for Glu and/or Gln.

It is unlikely that our Glu measurements reflect solely synaptic levels of this neurotransmitter, since the volume of brain tissue sampled also included cell bodies and processes of nonneuronal cells. Our measurements probably reflect an average of combined intra- and extracellular Glu levels arising from both neuronal and nonneuronal cells. A growing body of research over the last decade suggests that the Glu–Gln cycle between astrocytes and neurons may regulate synaptic activity (15). Interestingly, individuals with the greatest pain reduction also showed higher levels of Gln/Cr posttreatment, suggesting that our treatment intervention may have altered the Glu–Gln cycle.

Consistent with our observed changes in Glu functioning in evoked pain activity, we also detected changes in fMRI-determined BOLD activation that occurred in parallel to the dynamic Glu/Cr levels in the posterior insula. These data are consistent with the idea that neural activity is augmented within this region in FM (2,3). However, we found a differential relationship between Glu/Cr within the right posterior insula and changes in BOLD activity within the left insula compared with the right insula. This observation was unexpected, and may reflect the possibility that our intervention influenced the left and right insula in a differential manner. Alternatively, Glu levels may influence activation of the BOLD effect differentially during task conditions compared with resting conditions. Additional research will be required to further explore this finding.

Due to the small sample size used in our trial, these findings should be interpreted carefully. However, our data suggest that Glu may be a useful biomarker for disease severity in FM. Thus, future investigations of Glu within FM patient populations are warranted.

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AUTHOR CONTRIBUTIONS

Dr. Harris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Harris, Sundgren, Petrou, Gracely, Clauw.

Acquisition of data. Harris, Sundgren.

Analysis and interpretation of data. Harris, Pang, Hsu, Kim, McLean, Gracely, Clauw.

Manuscript preparation. Harris, Sundgren, Petrou, McLean, Gracely, Clauw.

Statistical analysis. Harris.

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Decreased Central μ -Opioid Receptor Availability in Fibromyalgia

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The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. Fibromyalgia (FM), a common chronic pain condition characterized by widespread pain, is thought to originate largely from altered central neurotransmission. We compare a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using μ -opioid receptor (MOR) positron emission tomography. We demonstrate that FM patients display reduced MOR binding potential (BP) within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR BP in the accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate and the striatum was also negatively correlated with the relative amount of affective pain (McGill, affective score/sensory score) within these patients. These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible reason for why exogenous opiates appear to have reduced efficacy in this population.

Key words: fibromyalgia; opioid; pain; chronic; positron emission tomography; μ

Introduction

Sensory perceptions can serve to alert organisms of present and/or future danger. This is particularly evident for the sensation of acute pain. However, neural pain pathways that originally function to warn of potential harm may also become dysfunctional and lead to maladaptive diseased states of a chronic nature (Woolf, 2004). Fibromyalgia (FM), a condition of idiopathic chronic pain, may be one such disorder.

FM is defined on the basis of tenderness and spontaneous chronic widespread pain (Wolfe et al., 1990) and afflicts 2–4% of individuals in industrialized countries (Wolfe et al., 1995). In addition many FM patients also suffer from psychiatric illnesses such as depression (Giesecke et al., 2003). Unfortunately, because of the lack of readily identifiable peripheral pathology in FM (e.g., muscle or joint inflammation), acceptance of this condition by medical practitioners has been slow (Cohen, 1999).

A growing body of scientific literature suggests that the lack of apparent peripheral pathology in FM might be explained by a primary disturbance in central rather than peripheral pain processing (Clauw and Chrousos, 1997). Data from psychophysical pain testing (Petzke et al., 2003), quantitative EEG (Lorenz et al.,

1996), and functional neuroimaging (Gracely et al., 2002; Cook et al., 2004) supports this theory. FM patients display increased neural activations in pain regions such as the insula, the somatosensory cortex, and the cingulate, in response to pressure pain. These same areas are activated in healthy control participants, albeit at higher objective stimulus intensities. Although this suggests that altered pain processing of experimental stimuli occurs in FM, the underlying neurobiology driving clinical symptoms such as pain and depression is unknown.

One potential reason for pain symptoms in FM may be inadequate descending antinociceptive activity. Research suggests that such activity may be deficient or absent in FM (Julien et al., 2005). In humans, the two principal descending inhibitory pain pathways involve either norepinephrine/serotonin or opioids, but psychophysical studies are incapable of distinguishing which of these pathways may be affected. FM patients display low CSF levels of biogenic amines, suggesting a possible deficiency of descending serotonergic/noradrenergic pathways in this condition (Russell et al., 1992). CSF levels of endogenous enkephalins, however, have been noted to be high, which suggests an excess of endogenous opioids in FM (Baraniuk et al., 2004). Although no trials of exogenous opioids in FM have been performed, opioids are not anecdotally found to be useful in treating this and related conditions (Rao and Clauw, 2004). Thus, existing data support a deficit in descending analgesic activity in the serotonergic/noradrenergic system and an overactive opioidergic system; however, as of yet, there is no direct evidence of this.

We used positron emission tomography (PET) to further investigate opioid antinociceptive activity in FM. [¹¹C]carfentanil, a selective μ -opioid receptor (MOR) radiotracer, was used to

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assess baseline receptor availability *in vivo* [binding potential (BP)] in patients and pain-free control participants. We hypothesized that patients with FM may have decreased MOR receptor availability, because they have increased levels of endogenous opioids in the CSF (Baraniuk et al., 2004), possibly leading to receptor downregulation. In addition, we investigated the association of MOR availability with both the affective and sensory dimensions of clinical pain. Finally, as an exploratory analysis, we examined the relationship between MOR availability and depression within FM patients.

Materials and Methods

Participants

As part of an ongoing study investigating the impact of acupuncture treatment in FM, 17 female right-handed patients (age, 44.8 ± 13.7 years; duration of FM diagnosis, 8.4 ± 6.0 years) were examined with PET. Seventeen right-handed age- and sex-matched control participants (age, 40.4 ± 11.2 years) were used as a comparison with the FM group. All analyses were performed on data acquired before acupuncture treatment. Participants gave written informed consent, and the study protocol was approved by the local Institutional Review Board and the Radioactive Drug Research Committee.

All patients (1) met the American College of Rheumatology 1990 criteria (Wolfe et al., 1990) for the diagnosis of FM for at least 1 year; (2) had continued presence of pain $>50\%$ of days; (3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; (4) were >18 and <75 years of age; (5) were female; (6) were right handed; (7) had no alcohol intake 48 h before PET studies; and (8) were capable of giving written informed consent. Patients were excluded if they (1) had used narcotic analgesics within the past year or had a history of substance abuse; (2) had presence of a known coagulation abnormality, thrombocytopenia, or bleeding diathesis; (3) had the presence of concurrent autoimmune or inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc., that causes pain; (4) had concurrent participation in other therapeutic trials; (5) were pregnant or nursing mothers; (6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, or substance abuse within 2 years); (7) had current major depression; or (8) had contraindications to PET. No patients were taking or had a previous history of opioid medication use. Ten of the FM participants were taking either serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors, whereas seven were not.

All healthy controls were (1) female; (2) right handed; (3) between the ages of 18 and 60; and (4) had no chronic medical illnesses.

Neuroimaging

Image acquisition. PET scans were acquired with a Siemens (Knoxville, TN) HR⁺ scanner in three-dimensional mode [reconstructed full-width at half-maximum (FWHM) resolution, ~ 5.5 mm in-plane and 5.0 mm axially], with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry, and an intravenous (antecubital) line was placed in the right arm. A light forehead restraint was used to eliminate intrascan head movement. [¹¹C]carfentanil was synthesized at high specific activity (>2000 Ci/mmol) by the reaction of [¹¹C]methyl iodide and a nonmethyl precursor as described previously (Dannals et al., 1985), with minor modifications to improve its synthetic yield (Jewett, 2001); 10–15 mCi (370–555 MBq) were administered during the scan. Receptor occupancy by carfentanil was calculated to be between 0.2 and 0.6% for brain regions with low, intermediate, and high MOR concentrations, based on the mass of carfentanil administered and the known concentration of opioid receptors in the postmortem human brain (Gross-Isseroff et al., 1990; Gablondo et al., 1995). Fifty percent of the [¹¹C]carfentanil dose was administered as a bolus, and the remaining 50% was administered by continuous infusion for the remainder of the study. Twenty-eight frames of images were acquired over 90 min with an increasing duration (30 s up to 10 min).

Anatomical magnetic resonance imaging (MRI) scans were acquired in all subjects on a 3 tesla scanner (Signa LX; General Electric, Milwaukee, WI). Acquisition sequences were axial SPGR IR-Prep magnetic resonance (MR) (echo time, 3.4 ms; repetition time, 10.5 ms; inversion time, 200 ms; flip angle, 20°; number of excitations, 1; number of contiguous images, 124; thickness, 1.5 mm).

Image processing. PET images were reconstructed using iterative algorithms (brain mode; FORE/OSEM, four iterations, 16 subsets; no smoothing) into a 128×128 pixel matrix in a 28.8 cm diameter field of view. Attenuation correction was performed through a 6 min transmission scan (⁶⁸Ge source) obtained before the PET study and with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image. Small head motions during emission scans were corrected by an automated computer algorithm for each subject before analysis, and the images were coregistered to each other with the same software (Minoshima et al., 1993). Time points were then decay corrected during reconstruction of the PET data. Image data were transformed on a voxel-by-voxel basis into two sets of parametric maps: (1) a tracer transport measure (K_1 ratio) and (2) a receptor-related measure at equilibrium [distribution volume ratio (DVR)]. To avoid the need for arterial blood sampling, the tracer transport and binding measures were calculated using a modified Logan graphical analysis (Logan et al., 1996), using the occipital cortex (an area devoid of MORs) as the reference region. The slope of the Logan plot was used for the estimation of the DVR, a measure equal to the $(f_2 B_{\text{max}}/K_d) + 1$ for this receptor site and radiotracer. $f_2 B_{\text{max}}/K_d$ (or $\text{DVR} - 1$) is the receptor-related measure (BP or MOR availability). The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value. K_1 and DVR images for each experimental period and MR images were coregistered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. The accuracy of coregistration and nonlinear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images to each other and the ICBM atlas template.

Group differences were mapped into stereotactic space using t maps of statistical significance with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) and Matlab (MathWorks, Natick, MA) software, with a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute $f_2 B_{\text{max}}/K_d$ estimates. Only regions with specific MOR BP were included in the analyses (i.e., voxels with DVR values >1.1). To compensate for small residual anatomic variations across subjects and to improve signal-to-noise ratios, a three-dimensional Gaussian filter (FWHM, 6 mm) was applied to each scan.

Image analysis. The comparisons between patients and control subjects were performed using two-sample t tests, on a voxel-by-voxel basis within SPM2. Significant effects were detected using a statistical threshold that controls a type I error rate at $p = 0.05$, corrected for multiple comparisons. These statistical thresholds were estimated using the Euler characteristic (Worsley et al., 1992) based on the number of voxels in the gray matter and image smoothness and the extent of local changes (correction for cluster volume) (Friston et al., 1991). Correlations between MOR BP and the relative amount of the affective quality of clinical pain were made using a regression model on a voxel-by-voxel basis with SPM2. Significant effects were detected using a cluster-corrected threshold p value of 0.05.

Numerical values for MOR binding were extracted from the image data by averaging the values of voxels contained in the area in which significant effects were obtained in the analyses. These values were then entered into SPSS version 14.0 (SPSS, Chicago, IL) for plotting, to rule out the presence of outliers, and to perform correlations with clinical measures.

Global BP values were also extracted and compared between groups with Student's t test. Because global values were found to be lower in the patients (see Results), global values were used as a covariate in regression analyses in which MOR BP was used as the dependent variable and group status and global BP were independent variables. This allows an estimate of group differences for a specific region, while controlling for differences

in global scores. To examine effects of concomitant drug usage in the patients, additional regression analyses were performed in which MOR BP was again used as the dependent variable and clinical pain and drug usage (either taking or not taking reuptake inhibitors; see above) were added as covariates. This final procedure was used to examine the effect of drug usage in the patient group on the relationship between MOR BP and pain.

Clinical assessment

Clinical pain. Clinical pain was assessed immediately before the PET scan with the Short Form of the McGill Pain Questionnaire (SF MPQ) (Melzack, 1987). The SF MPQ has two subscales that measure “sensory” and “affective” qualities of pain. To assess the relative contribution of the affective dimension of pain, the affective subscore of the SF MPQ was divided by the sensory subscore (affective/sensory). This yields an estimate of the relative contribution of the affective component of pain while controlling for the sensory intensity of the sensation (Petzke et al., 2005). For comparison, we also calculated the ratio of the sensory versus the affective subscores of the SF MPQ (i.e., sensory/affective).

Psychological assessment. Depressive symptoms were assessed with the Center for Epidemiological Studies–Depression Scale (Radloff, 1977). This is a 20-item self-report instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults in both clinical and normal populations. The total score was used for correlation with MOR BP.

Results

As expected, no significant differences were observed between the FM group and the control group with respect to participant age or sex (all $p > 0.05$). During PET imaging, FM patients exhibited significant reductions in MOR BP compared with controls in four regions: the bilateral nucleus accumbens (NAc; left, $p < 0.02$; right, $p < 0.05$; corrected for multiple comparisons), the left amygdala ($p < 0.05$; corrected for multiple comparisons), and the right dorsal anterior cingulate ($p < 0.05$; corrected for multiple comparisons) (Fig. 1A–C; Table 1). Global mean MOR BP values were reduced in the patient group ($p < 0.01$). Because a reduction in global BP value could explain the lower BP values within these regions for the FM participants, we performed regression analyses using regional MOR BP values as the dependent variable and group assignment and global BP as covariates. Both the left ($p < 0.001$) and right ($p < 0.05$) nucleus accumbens and the amygdala ($p < 0.005$) showed reduced MOR BP in the patients after controlling for global BP differences. The dorsal anterior cingulate showed a trend toward significance ($p < 0.07$). These data suggest that FM patients have reduced MOR BP within multiple brain regions.

To assess whether drug usage within the FM participants could be responsible for reduced MOR BP values, we examined the mean MOR BP for each of the above regions in FM participants that were either taking or not taking serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors. No differences in BP were detected for any of these regions between patients that were either taking or not taking this class of drugs (all $p > 0.35$). These analyses suggest that the reduced binding observed in the patients for these regions is not attributable to medication usage.

Within the FM patients, MOR BP binding in the left NAc was negatively correlated with clinical pain ratings in the affective (Fig. 2) (SF MPQ affective score, $r = -0.53$; $p < 0.05$) but not the sensory (SF MPQ sensory score, $r = -0.13$; $p > 0.50$) dimension of pain. Drug usage, when added as a covariate, did not significantly alter this relationship (standardized β without drug covariate = -0.44 ; with drug covariate, $\beta = -0.45$; significance of

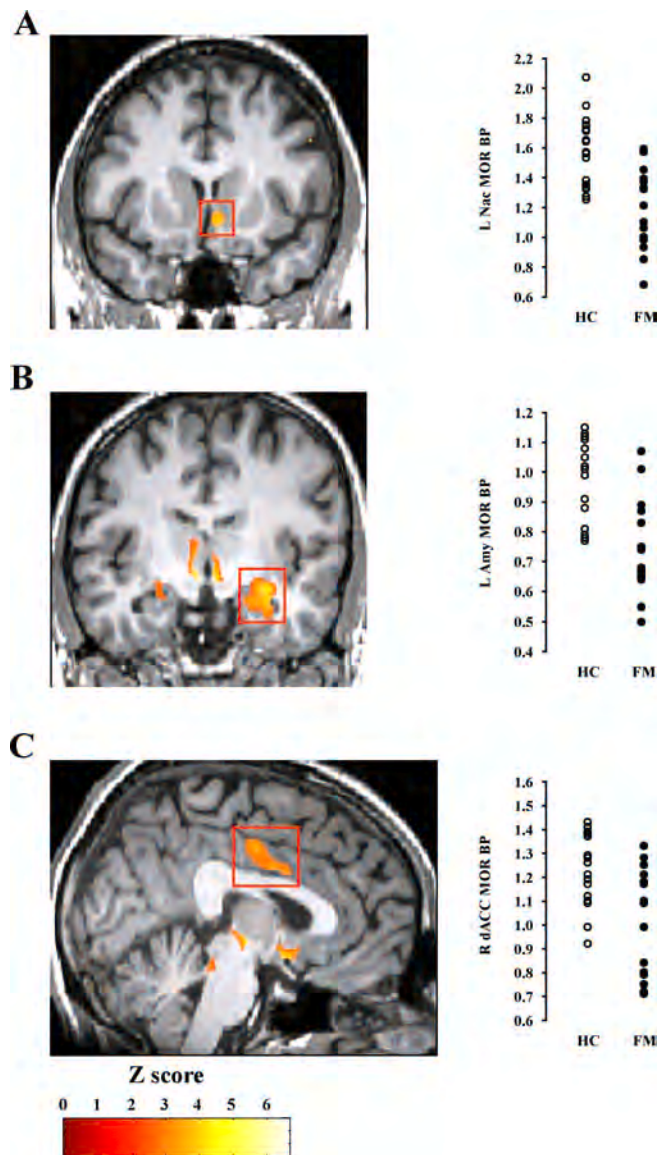


Figure 1. Reduced MOR BP in FM patients. **A–C**, Regions showing reduced MOR BP: left NAc (L NAc; **A**), left amygdala (L Amy; **B**), and right dACC (R dACC; **C**). Plots of individual MOR BP values extracted from PET images are depicted to the right of each corresponding region of interest. FM and healthy control (HC) participants are shown in black and white circles, respectively.

difference, $p = 0.59$). No statistically significant correlations were observed between clinical pain ratings and the right accumbens, the left amygdala, or the right dorsal anterior cingulate BP of FM patients (all $p > 0.05$). A significant negative correlation between MOR BP and depressive symptoms was also observed within the amygdala (Table 2).

Because MOR BP within the accumbens was associated with the affective dimension of pain, more so than the sensory dimension, we next investigated the relationship between MOR BP and the relative amount of affective versus sensory pain (SF MPQ, affective score/sensory score). Interindividual differences in MOR binding throughout the cingulate [dorsal anterior (dACC), $p < 0.05$; posterior (pACC), $p < 0.001$; and, to a lesser extent, anterior (aACC), $p = 0.09$; all corrected for multiple comparisons] were negatively correlated with the relative amount of affective pain (Fig. 3A,B, Table 3). Similar findings were detected within the right ventral putamen (Fig.

Table 1. Regions of reduced [^{11}C]carfentanil binding in FM patients

Brain region	MNI coordinates (x, y, z)	Z	Cluster size (mm ³)	% Δ Binding potential (HC – FM; mean \pm SD)
NAc (l)	9, 7, –11	4.1*	159	24.7 \pm 15.3
NAc (r)	–18, 6, –12	3.3*	140	18.1 \pm 13.3
Amygdala (l)	29, –10, –13	3.7*	269	23.7 \pm 14.6
dACC (r)	–4, –11, 43	3.1*	182	17.7 \pm 12.5

* $p < 0.05$, corrected. MNI, Montreal Neurological Institute; l, left; r, right.

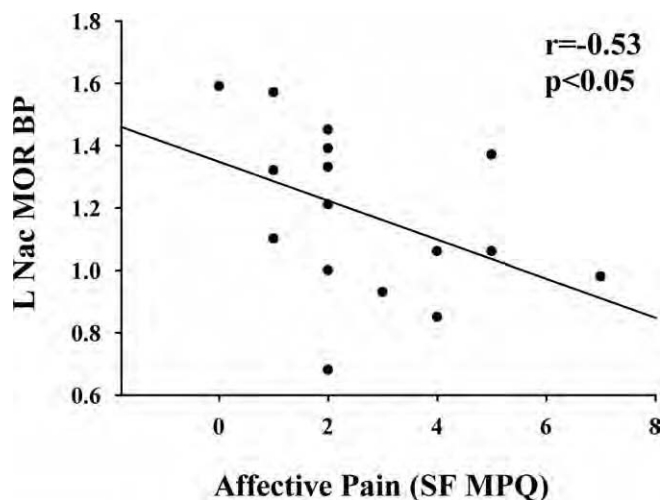


Figure 2. MOR BP is negatively correlated with affective pain. The scatter plot of left accumbens (L Nac) MOR BP and clinical pain (SF MPQ, affective score) reveals a significant negative correlation ($r = -0.53$; $p < 0.05$).

Table 2. Correlations between MOR availability and depression ratings in FM

Brain region	Rho value
NAc (l)	–0.25
NAc (r)	0.16
Amygdala (l)	–0.49*
dACC (r)	–0.21

* $p < 0.05$. l, Left; r, right.

3C). The primary somatosensory cortex and the insula also showed a negative correlation with MOR BP; however, these regions did not reach significance after correction for multiple comparisons ($p > 0.05$). Adding medication usage as a covariate did not significantly alter the relationship between affective/sensory scores and MOR BP for any of these regions (all percentage differences in standardized β s with and without covariate $\leq 1.3\%$; all significance of change, $p > 0.20$). No significant negative correlations were observed between MOR BP and the relative amount of sensory pain (SF MPQ, sensory score/affective score) within any brain regions (all $p > 0.05$). No correlations were observed between MOR BP within any of these regions and depressive symptoms (all $p > 0.20$). These results suggest that in FM patients the affective quality of pain is associated with reduced MOR availability throughout the cingulate and other brain regions commonly associated with pain modulation.

Discussion

Our data indicate that FM patients have reduced MOR BP within structures typically observed in imaging studies of experimental pain involving healthy control participants. These structures include the amygdala, the cingulate, and the nucleus accumbens.

All of these regions have previously been noted to play some role in nociception and pain. Opioid activity in the nucleus accumbens and the amygdala has been shown to modulate nociceptive neural transmission in animal models of pain (Gear and Levine, 1995; Manning, 1998). Indeed, endogenous opioids play a central role in analgesia and the perception of painful stimuli (Fields, 2004). MOR-mediated neurotransmission in the nucleus accumbens and amygdala has also been shown to be modulated by pain in healthy controls reducing the pain experience (Zubieta et al., 2001), in a manner consistent with animal data. Because the concentration of endogenous opioids is elevated in the CSF of FM patients (Baraniuk et al., 2004), MORs may be highly occupied by endogenous ligand in an attempt to reduce pain or downregulated after prolonged stimulation. Both these effects could explain the reduced MOR BP observed in this study.

An investigation using functional magnetic resonance imaging (fMRI) in FM has associated enhanced neural activity in both the amygdala and the cingulate with depressive symptoms (Giesecke et al., 2005). This further supports the notion that these regions may be involved with evaluating affective aspects of pain and is consistent with our findings of reduced MOR BP within the amygdala and its correlation with depressive symptoms. Indeed, the dorsal anterior cingulate region, identified as having reduced MOR BP in the patients, also showed a negative correlation with the affective dimension of pain (albeit in the opposite hemisphere). These data suggest that MOR availability within the dorsal anterior cingulate is related to the affective dimension of pain. This finding is supported by previous imaging studies of the cingulate (Vogt, 2005).

Two other chronic pain states, rheumatoid arthritis (Jones et al., 1994) and central neuropathic pain following stroke (Jones et al., 2004; Willoch et al., 2004), also display a reduction in opioid receptor BP within the CNS, as measured with the nonselective opioid receptor radiotracer [^{11}C]diprenorphine. Although these data may then suggest that reduced opioid receptor availability may be a shared feature across chronic pain states, the regional distribution of reduced receptor binding was dissimilar across these studies and pain conditions. In rheumatoid arthritis pain, reduced opioid receptor binding was observed in the cingulate, frontal, and temporal cortices, whereas for central neuropathic pain, reduced opioid receptor availability was detected primarily within the thalamus, somatosensory cortex, cingulate, and insula. In patients with peripheral neuropathic pain, reduced opioid BP has been observed bilaterally across brain hemispheres, whereas in central neuropathic pain, reductions in BP were observed largely isolated to one hemisphere (Maarrawi et al., 2007). This heterogeneous pattern of reduced binding may reflect different underlying mechanisms operating in these diverse pain conditions. In the case of FM the reductions in MOR BP observed were localized in regions known to be involved in antinociception in animal models (Gear and Levine, 1995; Manning,

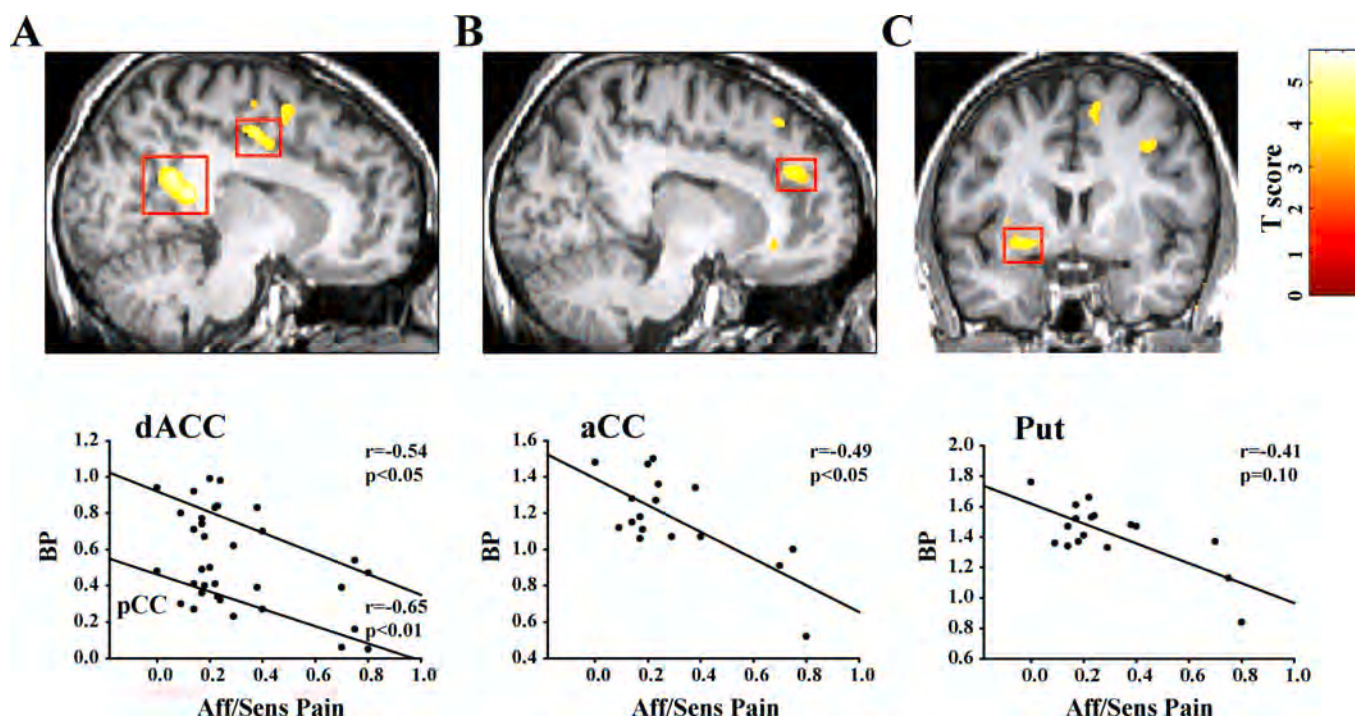


Figure 3. Relative magnitude of the affective pain dimension is associated with reduced MOR BP throughout the cingulate and striatum in FM. **A–C**, Regions showing significant correlations with SF MPQ affective/sensory (Aff/Sens) scores: left dACC and pCC (**A**), right aCC (**B**), and right putamen (Put; **C**). Scatter plots of individual MOR BP values extracted from PET images are plotted against affective/sensory scores below each image.

Table 3. Regions of correlated MOR BP and relative amount of affective versus sensory pain

Brain region	MNI coordinates (x, y, z)	Z	Cluster size (mm ³)	Rho value for extracted ROIs
dACC (l)	10, -11, 48	3.75**	1001	-0.54
pCC (l)	10, -44, 17	4.11***	936	-0.65
aCC (r)	-12, 38, 28	3.44*	410	-0.49
Putamen (r)	-26, 4, -8	3.36**	517	-0.41

* $p = 0.09$, corrected; ** $p < 0.05$, corrected; *** $p < 0.001$, corrected. MNI, Montreal Neurological Institute; ROIs, regions of interest.

1998), as well as pain and emotion regulation, including the affective quality of pain, in humans (Rainville et al., 1997; Zubieta et al., 2001, 2003) (i.e., dorsal anterior cingulate, nucleus accumbens, and amygdala).

Prolonged activations of the MOR by sustained elevations of endogenous agonist have been shown to result in a subsequent decrease in the concentration of MORs in animal models of chronic pain (Li et al., 2005). Chronic administration of morphine may reduce MOR functioning possibly by altering the ability of the receptor to bind to G-proteins, whereas other agonists also downregulate and internalize these receptors (Whistler et al., 1999). If this were the case in FM, sustained activation of MORs by endogenous agonists could ultimately lead to a downregulation of MOR receptor concentration, function, or both. Therefore both mechanisms (i.e., increased release of endogenous opioids and/or a reduction in receptor function) could be responsible for our findings.

We also observed a negative correlation between MOR BP within the accumbens and clinical ratings in the affective dimension of pain. This supports the hypothesis that mechanisms of clinical FM pain are coupled to MOR availability. A strong relationship between pain affect and MOR BP was also observed throughout multiple regions of the cingulate. This is consistent with a proposed role of the dorsal and anterior cingulate in the modulation of pain perception via opioidergic

mechanisms (Vogt et al., 1995). Recent investigations of opioid receptor binding in healthy controls showed reduced receptor availability within the rostral cingulate during thermal pain (Sprenger et al., 2006) and sustained muscular pain, which correlated with the suppression of pain affect (Zubieta et al., 2001). Within animal models of experimental pain, microinjection of morphine into the anterior cingulate dose-dependently reduced affective components of pain greater than sensory aspects (LaGraize et al., 2006). Our findings of greater affective pain associated with lower MOR BP within the cingulate are consistent with these observations.

We also detected a negative correlation between affective pain and MOR BP values within the posterior cingulate. This is potentially a novel finding because this region is not typically observed in pain imaging trials in humans (Vogt, 2005). However previous trials do suggest that activity within the posterior cingulate, specifically the dorsal aspect, is related to skeletomotor orientation of the body in response to noxious stimuli (Vogt, 2005; Vogt and Laureys, 2005). Because our FM participants experienced clinical pain during the scanning sessions, one could speculate that reduced MOR BP within this region may reflect activation of the endogenous opioid system in an attempt to reduce skeletomotor orientation resulting from spontaneous clinical pain. One additional potential lim-

itation of this final analysis is that affective and sensory pain dimensions are often highly correlated.

A significant relationship was also detected between MOR availability within the amygdala and depression. Individuals with more depressive symptoms had reductions in MOR BP within the amygdala. This finding is not unexpected, because reduced opioid receptor availability within the amygdala has been previously associated with periods of sadness in patients with major depressive disorder (Kennedy et al., 2006).

Perhaps more important for clinical investigations in FM, our results would predict a lack of efficacy for exogenous opioids in this population. Regardless of whether endogenous opioids are high (Baraniuk et al., 2004) or MORs are down-regulated, both scenarios would predict that FM patients would respond less well to exogenous opioids. This prediction awaits future prospective trials of exogenous opioid treatments in FM.

Overall we detect decreased MOR availability in FM patients, demonstrating a dysregulation of this neurotransmitter system in this disease. The reduction in binding was further negatively correlated with affective pain. The observation of specific regional alterations in central opioid neurotransmission in FM suggests that these mechanisms, possibly as a consequence of persistent pain, are involved in the clinical presentation and even the perpetuation of symptoms in this illness. Furthermore, because these receptors are the target of opiate drugs, a profound reduction in the concentration or function of these receptors is consistent with a poor response of FM patients to this class of analgesics, observed anecdotally in clinical settings.

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Abstract/Presentations

Human Brain Mapping Conference

June 18-24, 2009

San Francisco, CA

International Conference on the Mechanisms and Treatment of Neuropathic Pain

November 6-8, 2008

Bermuda

Medical Acupuncture in Integrative Care

August 2-3, 2008

Singapore

American College of Rheumatology

October 24-28, 2008

San Francisco, CA

International Association for the Study of Pain

12th World Congress on Pain

August 17-22, 2008

Glasgow, Scotland, UK

American Pain Society

27th Annual Scientific Meeting

May 8-10, 2008

Tampa, FL

INTRINSIC RESTING BRAIN NETWORKS ARE ASSOCIATED WITH SPONTANEOUS PAIN IN CHRONIC FUNCTIONAL PAIN PATIENTS

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Introduction

Chronic functional pain (CFP) syndromes are associated with abnormal brain responses to experimental noxious stimuli^{1,2}, however neurobiological correlates of patients' known spontaneous clinical pain³ remain elusive. As default-mode network (DMN) response has been found to be disrupted in chronic pain patients⁴, we hypothesized that resting DMN activity in CFP patients would be abnormal and associated with spontaneous clinical pain report. Furthermore, resting fMRI connectivity to the anterior insula cortex (AIC), a region whose resting fMRI signal is typically anti-correlated to DMN activity and which has augmented activity in CFP patients^{1,2}, might also be linked to spontaneous pain.

Methods

Resting fMRI data (3.0 T GE scanner, TR/TE=2000/30ms, 3.13x3.13x4.0mm, runtime=360s) were acquired from 12 CFP patients (7 fibromyalgia, 5 chronic pelvic pain) and 7 healthy controls (HC). Probabilistic Independent Component Analysis (p-ICA, MELODIC, FSL) was performed on the fMRI data. The best-fit DMN independent component was found with a spatially-focused template matching algorithm. Group main effect maps for both CFP and HC, as well as a difference map were calculated. An analysis of covariance (ANCOVA) was performed to yield CFP brain regions where DMN connectivity covaried with the patients' pain intensity reported immediately prior to the MRI scan. AIC Seed connectivity was also evaluated. Individual patients' seeds were chosen as the 20%⁵ most anti-correlated voxels to the DMN within an anatomically defined AIC mask. A conjunction analysis was then performed to find a seed mask which accounted for the majority of CFP patients. Each patients' resting AIC connectivity map was then calculated and used in an ANCOVA with pain scores. All group analyses used mixed-effects (FLAME, FSL) and thresholded at cluster-corrected $p < 0.05$.

Results

The DMN for CFP patients demonstrated greater connectivity in the precuneus, and less connectivity in the dorsomedial prefrontal cortex, compared to HC. Furthermore, in CFP patients, connectivity to the DMN was positively correlated with pain intensity in the pre-supplementary motor cortex (pre-SMA), pontine raphe nuclei, and right primary sensorimotor cortex (SI/M1), while DMN connectivity to the fronto-insular cortex and precuneus was negatively correlated (Figure 1). Also in CFP patients, connectivity to the AIC was positively

correlated with pain in the amygdala, orbitofrontal cortex (OFC), and middle temporal gyrus and negatively correlated with SMA, premotor, and SI/M1 (Figure 2).

Conclusions

These results suggest a complex interplay between resting brain networks and pain symptoms in CFP patients. Increased spontaneous pain is associated with greater connectivity between DMN and sensorimotor processing brain regions as well as the pontine raphe. Thus, these regions may be linked to descending facilitation in CFP patients. In turn, greater DMN connectivity in the precuneus may be a successful coping strategy for CFP patients, as lower pain scores were associated with greater DMN/precuneus connectivity. Furthermore, the AIC, a region previously noted to encode pain affect⁶, was more connected with other affective pain regions such as the amygdala and OFC, when pain scores were high. Resting functional connectivity may prove to be a viable assay for the spontaneously fluctuating endogenous chronic pain, which has been notoriously difficult to image.

¹ Gracely et al. Arthritis and Rheumatism 2002

² Cook et al. Journal of Rheumatology 2004

³ Harris et al. Arthritis and Rheumatism 2005

⁴ Baliki et al. J Neurosci 2008

⁵ Mitsis et al. Neuroimage 2008

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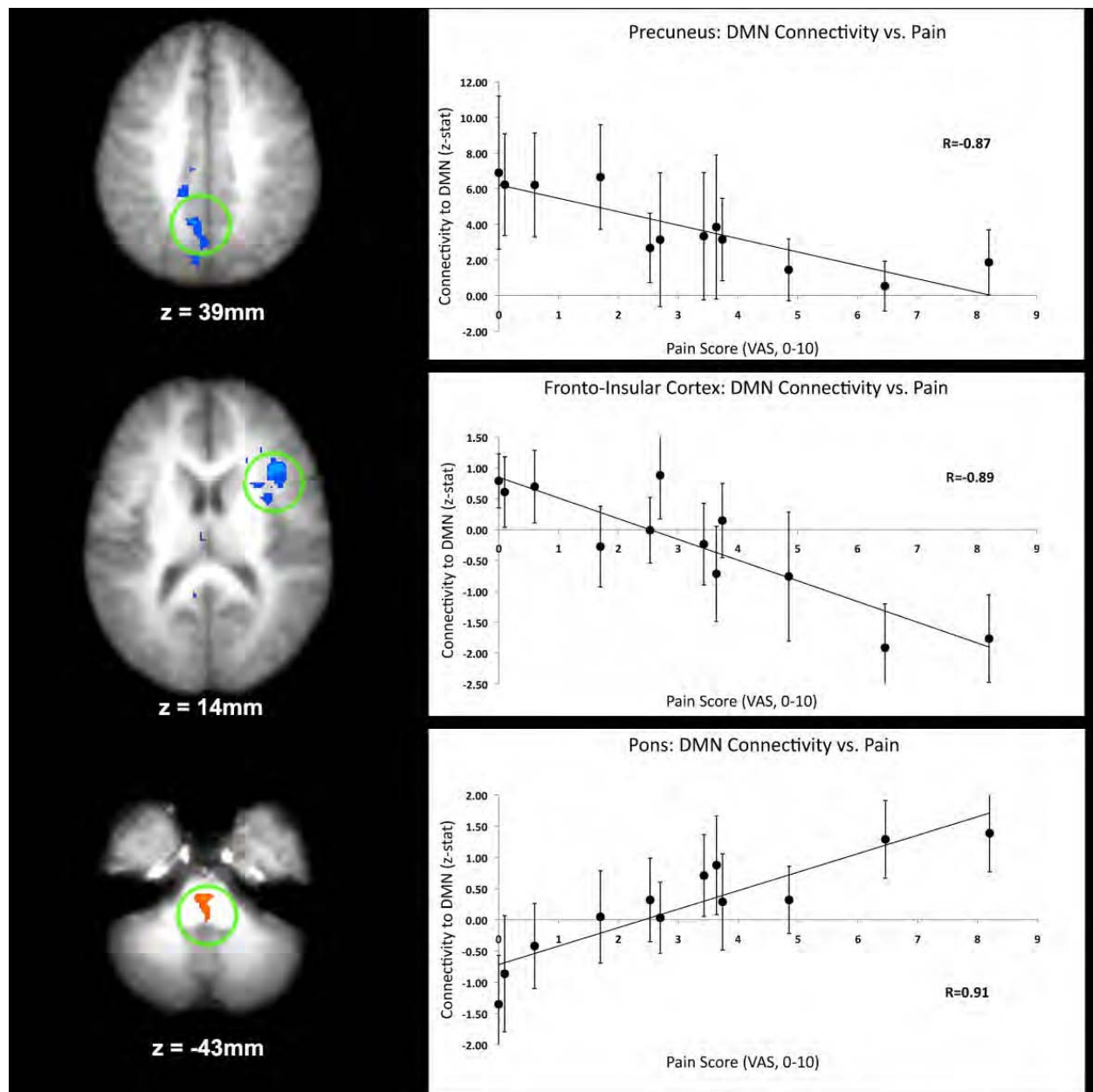


Figure 1: An Analysis of Covariance demonstrated that CFP patients in greater pain had greater DMN connectivity with pontine raphe nuclei, and lesser DMN connectivity with the fronto-insular cortex and precuneus.

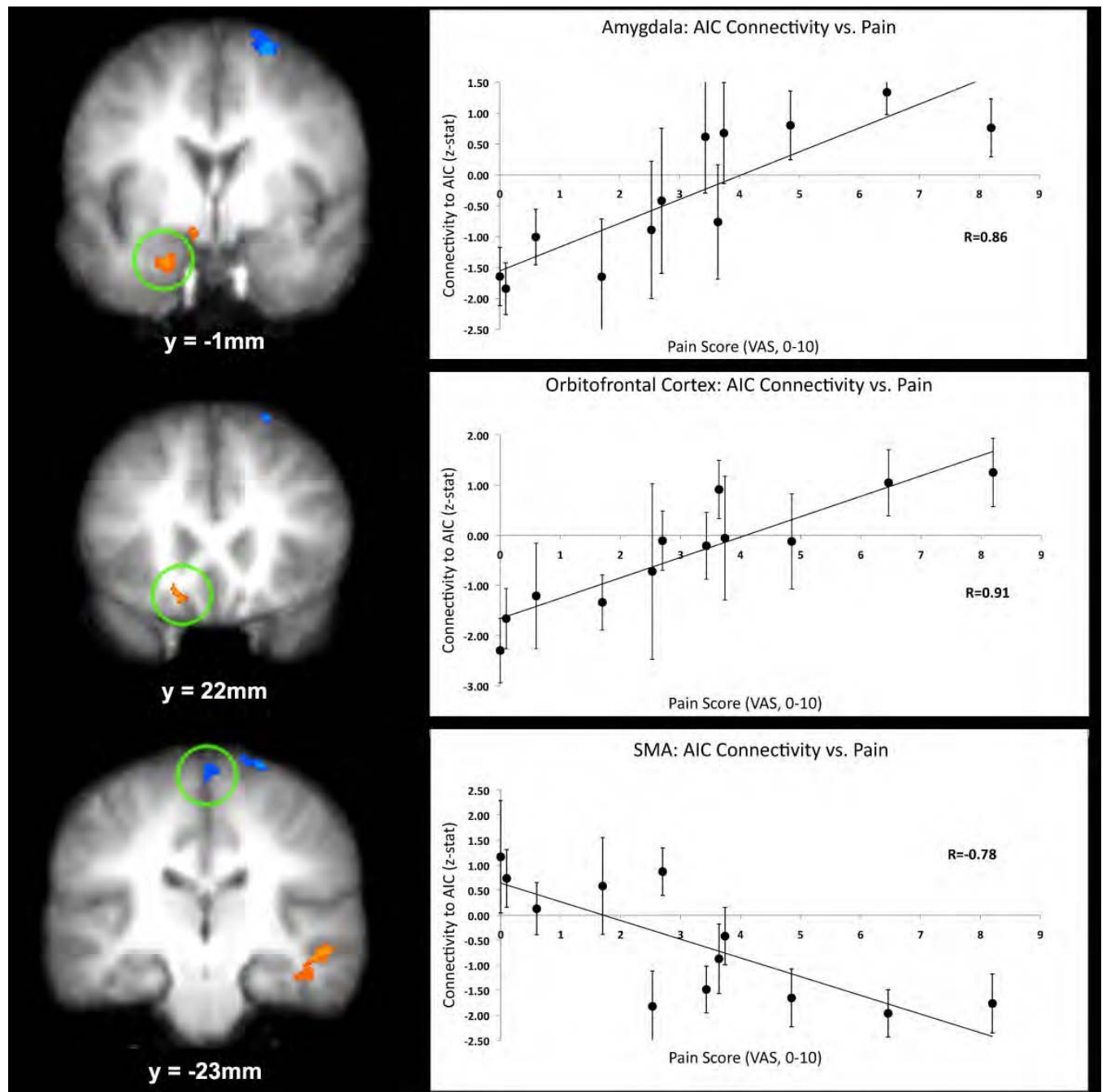


Figure 2: An Analysis of Covariance demonstrated that CFP patients in greater pain had greater AIC connectivity with the amygdala and orbitofrontal cortex, and lesser AIC connectivity with the supplementary motor area.

VARIATION IN GLUTAMATE AND GLUTAMINE LEVELS WITHIN THE ANTERIOR INSULA ARE ASSOCIATED WITH CHANGES IN ANXIETY AND PAIN IN FIBROMYALGIA (FM)

Richard E. Harris, Pia C. Sundgren, Eric Kirshenbaum, Zhe Xiang, and Daniel J. Clauw

Purpose: The insula is thought to be involved in processing both sensory and affective aspects of pain. The anterior region is thought to encode affective qualities of pain and/or mood, and the posterior region is believed to process more of the sensory dimension of pain. Our previous proton magnetic resonance spectroscopy (H-MRS) study suggested that reductions in the sensory dimension of pain were associated with decreased glutamate (Glu) levels in the posterior insula of FM patients (Harris et al. Arthritis and Rheumatism 2008). Here we examine the relationship between changes in Glu levels within the anterior insula and changes in mood and pain in FM patients.

Methods: As part of an ongoing trial of acupuncture in FM, 14 patients (42 \pm 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. SVS sequences were performed with the VOI placed first in the right anterior insula and patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cr; eg. Glu/Cr). Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form of the McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. State-anxiety was also assessed with the State-Trait Personality Inventory (STPI) scale pre- and post-treatment. Data were analyzed with SPSS v.14.

Results: There was a trend for clinical and experimental pain to improve over the course of treatment (SF-MPQ Mean Diff(SD): Total=6.78(13.6), $p=0.09$; Sensory=3.57(7.3), $p=0.09$; Affective=1.29(2.5), $p=0.07$; high pain threshold kg: -0.58(1.0), $p=0.06$), however anxiety did not improve ($p>0.30$). Glu/Cr, Gln/Cr, and Glx/Cr levels did not significantly change over time (all $p>0.05$), but differences in Glu/Cr (pre-post treatment) within the anterior insula were positively correlated with changes in the affective dimension of pain and anxiety (Affective: $r=-0.60$; $p=0.02$; Anxiety: $r=0.73$; $p=0.008$). Changes in Gln/Cr levels within the anterior insula were also negatively correlated with changes in anxiety ($r=-0.87$; $p<0.001$). Inter-individual variations in Glu/Cr were not correlated with changes in hyperalgesia (all thresholds: $p>0.5$).

Conclusion: Glu and/or Gln levels in the anterior insula are associated with changes in the affective dimension of pain and mood in FM patients. This could result from changes in glutamatergic neurotransmission within this structure.

Acknowledgements: Funding for this study came from Department of Army grant DAMD-17/002-0018 and NIH/NCRR grant M01-RR000042. REH was supported by a grant from the NIH/NCCAM K01 AT01111-01 and Department of Army award PR064072.

DIFFERENCES IN CENTRAL NEURAL PAIN PROCESSING FOLLOWING ACUPUNCTURE AND SHAM ACUPUNCTURE THERAPY IN FIBROMYALGIA (FM)

Ann Poznanski, Michael Hsu, Richard H. Gracely, Daniel J. Clauw, and Richard E. Harris

Clinical trials of acupuncture for the treatment of chronic pain conditions such as fibromyalgia (FM) have resulted in equivocal findings. In most studies, traditional acupuncture and sham acupuncture are equally effective. However no study has used functional magnetic resonance imaging (fMRI) in FM patients to examine more detailed changes in central pain processing following traditional and sham acupuncture. 25 female FM participants were randomized to receive either 9 sessions of traditional Chinese acupuncture (TA; $n=13$; mean(SD)age=48.9(11.3)yrs) or 9 sessions of sham acupuncture (SA; $n=12$; mean(sd)age=42.9(13.6)yrs) over the course of one month. Neural activity evoked by painful pressures applied to the thumbnail was assessed pre- and post-treatment with fMRI. Clinical pain was assessed with the Short Form of the McGill Pain Questionnaire (SFMPQ) and experimental pressure pain sensitivity was assessed pre- and post-treatment. The entire cohort displayed reductions in both clinical and experimental pain (SFMPQ total mean(SD)change=5.15(5.65), $p=0.001$; mild pressure pain threshold mean(SD)change kg=0.58(0.85), $p=0.003$), however no significant differences in the amount of pain reduction were detected between groups for either pain dimension (both $p>0.15$). Significant differences in pain evoked neural activity were detected between TA and SA for the inferior parietal lobule ($Z=3.5$; $p<0.001$ uncorrected) and two regions in the cerebellum (region 1: $Z=3.08$; $p=0.001$ uncorrected; region 2: $Z=3.2$; $p<0.001$ uncorrected). In these regions greater reductions in pain evoked activity were detected following TA. Other regions within the cerebellum and the posterior cingulate showed trends towards greater reductions following TA ($p<0.002$ uncorrected). No regions were detected that showed greater reductions in neural activity following SA. Although both TA and SA resulted in similar reductions in pain report, fMRI was able to detect differences between these two treatments. fMRI may more sensitive at detecting changes in pain processing than subjective pain report.

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CENTRAL μ -OPIOID RECEPTOR (MOR) AVAILABILITY COVARIES WITH MOOD STATE AND PAIN IN FIBROMYALGIA (FM)

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Fibromyalgia (FM) is a chronic widespread pain condition that is often accompanied by comorbid negative mood states including stress and depression. Positron emission tomography (PET) studies have demonstrated alterations in central μ -opioid receptor (MOR) availability in fibromyalgia patients as well as patients diagnosed with major depressive disorder. However, the regulation of the endogenous opioid system in the experience of negative mood states and pain within the same individuals is less well understood. Using PET to label MORs, we examined the correlation between the availability of MORs in the brain and self reported mood and pain in 20 fibromyalgia patients (49.5(13.2)yrs). Mood and pain were assessed by the Positive and Negative Affectivity Scale (PANAS) and the Short Form of the McGill Pain questionnaire respectively. Negative affect was positively correlated with MOR binding potential (BP; an *in vivo* measure of receptor availability) in anterior cingulate cortex (ACC: $r=0.77$; $p<0.001$), insula ($r=0.67$; $p=0.001$), hippocampus ($r=0.67$; $p=0.001$) and middle frontal cortex ($r=0.75$; $p<0.001$). Within these regions, clinical pain was positively correlated with MOR BP only in the ACC ($r=0.58$; $p<0.01$) and insula ($r=0.56$; $p=0.01$). Linear regression analyses, demonstrated that MOR BP in the ACC was independently correlated with both negative affect (Beta 0.64; $p<0.001$) and pain (Beta 0.33; $p=0.04$). These data demonstrate that MOR availability is associated with pain and negative affect in FM patients albeit in partially overlapping brain regions.

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DIFFERENTIAL SUSTAINED CHANGES IN μ -OPIOID RECEPTOR (MOR) AVAILABILITY FOLLOWING ACUPUNCTURE AND SHAM ACUPUNCTURE THERAPY IN FIBROMYALGIA (FM)

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Objective: Clinical trials of acupuncture versus sham therapy in fibromyalgia (FM) have had equivocal findings. Since MORs are thought to be involved in both acupuncture analgesia and placebo effects, we investigated changes in central MOR availability following these interventions using positron emission tomography (PET) in FM.

Materials and Methods: 17 female FM patients were randomized to receive either nine traditional acupuncture (TA; n=9) or nine sham acupuncture (SA; n=8) treatments over four weeks. PET imaging with [¹¹C]-carfentanil, a selective MOR agonist, was performed pre- and post-treatment. Changes in MOR binding potential (BP) were compared between groups using SPM99. Clinical pain was measured with the Short Form McGill Pain Questionnaire (SF MPQ).

Results: Clinically significant improvements in pain were obtained following treatment (SF MPQ: MeanDiff(SD) TA=5.4(9.6); SA=2.3(6.4)) although there was no difference between groups (p=0.44). However significant changes in MOR BP were detected between TA and SA within 17 different brain regions (all p<0.001; uncorrected) including the: insula, amygdala, thalamus, cingulate, caudate, prefrontal cortex, and hypothalamus. Within the anterior cingulate improvements in clinical pain were positively correlated with increases MOR BP for TA (r=0.68; p=0.04) but negatively for SA (r=-0.81; p=0.02). Within the caudate improvements in clinical pain were positively correlated with increases in MOR BP for TA (r=0.75; p=0.02) but not SA (p>0.90).

Conclusion: The underlying mechanisms of TA and SA are not equivalent, despite similar effects on clinical pain report. Further studies using larger samples will be necessary to corroborate these findings.

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VARIATION IN GLUTAMATE AND GLUTAMINE LEVELS WITHIN THE INSULA ARE ASSOCIATED WITH IMPROVEMENTS IN CLINICAL AND EXPERIMENTAL PAIN IN FIBROMYALGIA (FM)

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Richard H. Gracely, and Daniel J. Clauw

Purpose: The insula is involved in processing both sensory and affective aspects of pain. Previous functional neuroimaging studies suggest augmented neural activity within this structure in FM patients. Since glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, we used proton magnetic resonance spectroscopy (H-MRS) to investigate variations in Glu and glutamine (Gln) levels over time in FM patients. We hypothesized that reductions in Glu and/or Gln should parallel improvements in clinical pain and evoked pain sensitivity.

Methods: As part of an ongoing trial of acupuncture in FM, 10 patients (48 \pm 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Two separate SVS sequences were performed with the VOI placed first in the anterior and then the posterior insula. Patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cre; eg. Glu/Cre). Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form of the McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. Data were analyzed with SPSS v.14.

Results: Clinical pain improved over the course of treatment for the sensory but not the affective dimension of pain (SF-MPQ Mean Diff(SD): Sensory=3.5(4.7); $p=0.04$; Affective=0.1(2.5); $p>0.05$). Hyperalgesia was also significantly reduced at moderate pressures (Mean Diff(SD)=-0.34(0.46)kg; $p=0.04$). Glu/Cre, Gln/Cre, and Glx/Cre levels did not significantly change over time (all $p>0.05$), but differences in Glx/Cre and Glu/Cre (pre-post treatment) within the posterior insula were negatively correlated with changes in hyperalgesia (Glx/Cre: $r=-0.68$; $p=0.03$; Glu/Cre: $r=-0.93$; $p<0.001$). Changes in Glx/Cre levels within the anterior insula were also negatively correlated with changes in hyperalgesia ($r=-0.77$; $p=0.04$). Inter-individual variations in Glu/Cre within the posterior insula were also positively correlated with changes in clinical pain (McGill total: $r=0.80$; $p=0.005$; Sensory: $r=0.77$; $p=0.009$; Affective: $r=0.78$; $p=0.008$).

Conclusion: Insular Glu and/or Gln levels appear to change with improvements in multiple pain dimensions within FM patients. This could result from changes in glutamatergic neurotransmission within this structure. H-MRS may be a useful outcome measure in clinical trials within this population.

DIFFERENCES IN REGIONAL GRAY-MATTER DENSITY BETWEEN FIBROMYALGIA PATIENTS AND CONTROLS: A VOXEL-BASED MORPHOMETRY STUDY

Michael C. Hsu, Richard E. Harris, Carlo Fernandes, Robert C Welsh, Pia M. Sundgren, Daniel J. Clauw

Fibromyalgia (FM) is thought to involve abnormalities in central pain processing, and recent studies on small numbers of subjects have suggested reductions in gray-matter density in patients with FM. Our objective was to search for regional differences in gray-matter density between FM patients and controls, and to determine whether the gray-matter density in such regions correlates with pressure-pain threshold and duration of symptoms. We used a cross-sectional, case-control design involving 51 FM patients and 51 age-matched healthy controls. Our primary outcome measure was regional gray-matter density as estimated by voxel-based morphometry on high-resolution T1-weighted MRI brain images. We performed both a whole-brain volume search corrected for multiple comparisons, followed by region-of-interest (ROI) search using ROIs defined *a priori*. We extracted signal intensities from these ROIs and correlated them with pressure-pain threshold to the left thumbnail (Multiple Random Staircase method) and baseline pain intensity (Brief Pain Inventory average pain or VAS present pain). Decreased gray-matter density was observed in the left anterior insula (MNI coordinates {-24,19,-15}) in FM patients relative to age-matched healthy controls (pFWE = 0.056, small-volume correction,). No other ROIs showed significant gray-matter density differences between groups. In exploratory analyses we investigated a previously-reported contrast between left and right insula with respect to pain processing. In the entire group of subjects, the signal intensity difference between left and right posterior insula correlated significantly with both medium and high pressure-pain thresholds ($r = -.234$, $p = .018$; $r = -.232$, $p = .019$; respectively). This is the largest study to date comparing regional gray-matter density between FM patients and age-matched controls. Subjects with FM seem to exhibit a reduction in gray-matter density in the left anterior insula, but unlike previous studies with fewer subjects, no other significant regional differences were found.

DATA-DRIVEN PARCELLATION OF THE INSULAR CORTEX USING RESTING-STATE fMRI

Scott J. Peltier, Michael C. Hsu, Robert C. Welsh, Rupal Bhavsar, Laura, Yang, Richard E. Harris, Daniel J. Clauw, David A. Williams.

Introduction

Previous studies have shown that insular cortex is important in pain processing. The majority of studies have used functionally or anatomically-defined regions of interest (Taylor 2009). However, data-driven approaches have been used to examine resting-state fMRI functional connectivity (Peltier 2003), and may have utility in identifying functionally-distinct areas within the insula. In this work, we applied a data-driven approach to parcellate the insular cortex into anterior, middle and posterior regions.

Methods

Acquisition: As part of an ongoing clinical trial at the University of Michigan, 17 healthy controls and 29 fibromyalgia patients were scanned in a 3 T GE scanner. All subjects were right-handed women. A T2*-weighted spiral-in acquisition was used (TR/TE/FA/FOV = 2.5s/30ms/90/22cm, 64x64 matrix), to acquire 43 slices. 144 timepoints were acquired, for a total scan time of 6 minutes, during which subjects to instructed to lie quietly while being presented with a visual fixation cross.

Analysis: Time series data were processed using physiological and slice-time correction; sessions containing excessive motion (>4 mm translation, $>.1$ degree rotation) were eliminated. Data were then normalized to the MNI template and smoothed with a 5mm FWHM kernel using SPM2 (reference). Data were then low-pass filtered (0.08 Hz cutoff) to analyze those frequencies important for BOLD functional connectivity (Cordes).

The data was then masked using an insula cortex mask generated from Marsbar Region of Interest Toolbox (Brett 2002). A self-organizing map (SOM) MATLAB toolbox (Welsh 2007) was used to parcellate the bilateral insular data of the control subjects into 9 clusters. The resulting cluster maps were then compared for anatomical overlap between subjects, with consistent areas defined as those voxels shared by $\geq 80\%$ of control subjects.

Results

Consistent clusters in R and L anterior insula, bilateral middle insula, and L posterior insula were observed in the control data (Fig 1).

Maxima from the one-sample t-test across all subjects are given in Table 1, which compare well with recent seed-based literature (Taylor 2009).

Conclusions

Data-driven parcellation of the insular cortex was achieved. Consistent regions of activity were found across a group of healthy control and fibromyalgia patients. This should provide the basis for unbiased analysis of the insular cortex between clinical groups.

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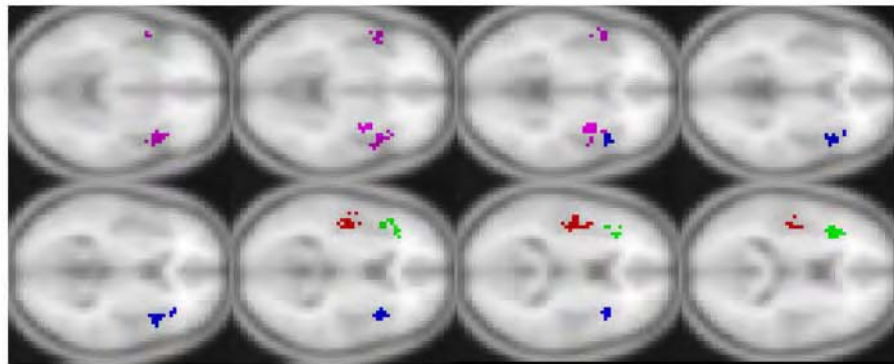


Figure 1. Consistent insula clusters identified in the SOM analysis, overlaid on the standard SPM T1 template. Green: Left anterior, Red: Left posterior, Blue: Right anterior, Magenta: Bilateral middle.

Region	ROI maxima coordinate (MNI)		
	x	y	z
Left anterior	-33	18	12
Left posterior	-45	-12	9
Bilateral middle	42	18	-3
Right anterior	45	15	0

Table 1. ROI maxima from the one-sample t-test for each cluster.

VARIATION IN GLUTAMATE AND GLUTAMINE LEVELS WITHIN THE INSULA ARE ASSOCIATED WITH IMPROVEMENTS IN WORKING MEMORY IN FIBROMYALGIA (FM)

Jennifer M. Glass, Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Richard H. Gracely, and Daniel J. Clauw

Purpose: The insular cortex is involved in processing both sensory and affective aspects of pain and more generally is believed to integrate sensory and affective information. Additionally, the insula is involved in language processing, particularly the articulatory loop that is part of the working memory system, and FM patients show working memory impairments. Previous functional neuroimaging studies suggest augmented neural activity within this structure in FM patients. Since glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, we used proton magnetic resonance spectroscopy (H-MRS) to investigate variations in Glu and glutamine (Gln) levels over time in FM patients. We hypothesized that changes in Glu and/or Gln should parallel improvements in working memory performance.

Methods: As part of an ongoing trial of acupuncture in FM, 10 patients (48 \pm 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Two separate SVS sequences were performed with the VOI placed first in the anterior and then the posterior insula. Patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cre; eg. Glu/Cre). Working memory was assessed pre- and post-treatment with the Letter-Number span test from the Wechsler Memory Scale. Data were analyzed with SPSS v.14.

Results: Working memory performance improved post-treatment. Glu/Cre, Gln/Cre, and Glx/Cre levels did not significantly change over time (all $p>0.05$). Differences in Gln/Cre (pre-post treatment) within the posterior insula were negatively correlated with changes in working memory (Gln/Cre: $r=-0.778$, $p=0.008$). Changes in Glx/Cre levels within the anterior insula were positively correlated with changes in working memory ($r=0.701$, $p=0.024$).

Conclusion: Changes in Insular Glu and/or Gln to Cre ratios correlate with improvements in working memory within FM patients. Specifically, increased Gln/Cre ratio in the anterior insula were associated with larger improvements in working memory. This could result from changes in glutamatergic neurotransmission within the part of the insula that is involved in the articulatory loop. In contrast, decreased ratio of Glx/Cre in the posterior insula were associated with larger improvements in working memory, perhaps due to decreased affective interference. These data are the first to associate Glu and Gln levels with working memory function in FM. H-MRS may be a useful outcome measure in clinical trials within this population.

Title: No Difference in Gray Matter Volume between Fibromyalgia Patients and Age-Matched Healthy Subjects when Controlling for Depressive Disorder

Authors: Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, Williams DA

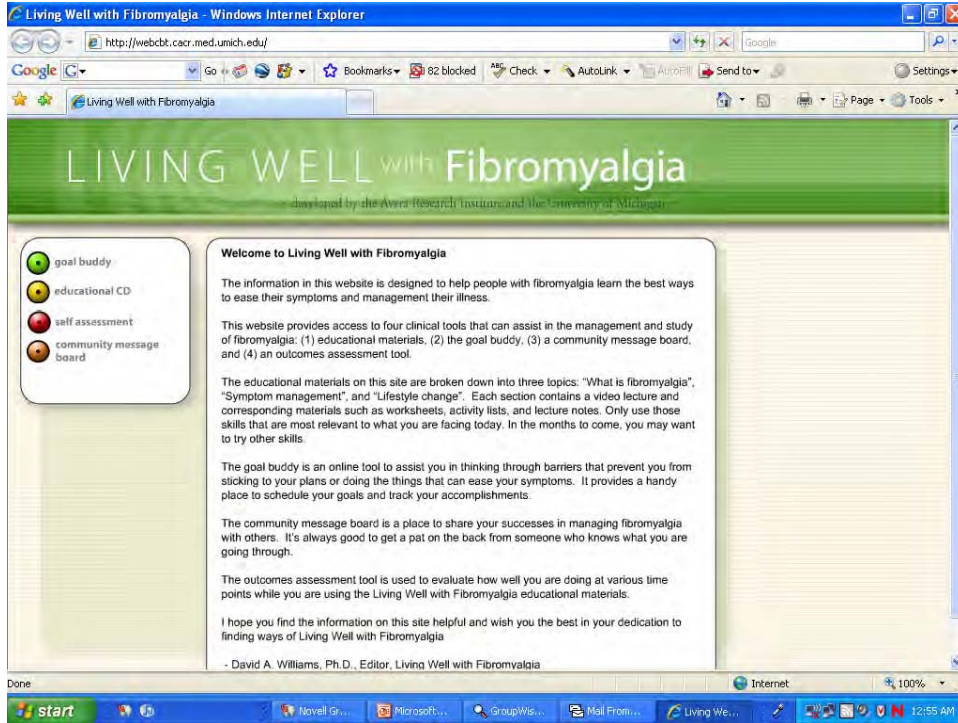
ABSTRACT

Fibromyalgia (FM) is thought to involve abnormalities in central pain processing. Recent studies involving small samples have suggested alterations in gray matter volume (GMV) in brains of FM patients. Our objective was to verify these findings in a somewhat larger sample using voxel-based morphometry (VBM), while controlling for presence of affective disorders (AD). T1-weighted magnetic resonance image (MRI) brain scans were obtained on 29 FM patients with AD, 29 FM patients without AD, and 29 age-matched healthy controls (HC) using a 3T scanner. Segmentation, spatial normalization, and volumetric modulation were performed using an automated protocol within SPM5. Smoothed gray matter segments were entered into a voxel-wise one-way ANOVA, and a search for significant clusters was performed using thresholding methods published in previous studies (whole-brain threshold of $p < .05$ correcting for multiple comparisons; region-of-interest (ROI) threshold of $p \leq .001$ uncorrected, or $p < .05$ small-volume corrected). The whole-brain analysis did not reveal any significant clusters. ROI-based analysis revealed a significant difference in left anterior insula GMV among the three groups ($xyz = \{-28, 21, 9\}$; $p = .026$, corrected). However, on post-hoc testing, FM patients without AD did not differ significantly from HC with respect to mean GMV extracted from this cluster. A significant negative correlation was found between mean cluster GMV and scores of trait anxiety (State-Trait Personality Inventory, Trait Anxiety scale; $\rho = -.470$, $p < .001$). No other significant clusters were found on ROI-based analysis. Our results emphasize the importance of correcting for AD when carrying out VBM studies in chronic pain.

Screenshots

Living Well with Fibromyalgia CD

*Internet and Telehealth Enhanced CBT
for the Management of Fibromyalgia*



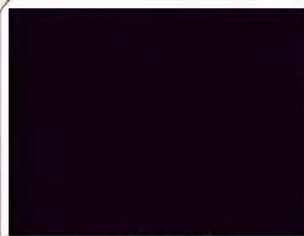
LIVING WELL with Fibromyalgia

developed by the Avera Research Institute and the University of Michigan

- what is fibromyalgia?
 - about fibromyalgia?
 - what causes fibromyalgia?
 - treatment advice

- symptom management
 - medications
 - exercise
 - sleep
 - relaxation ▶
 - pleasant activity

- lifestyle change
 - goal setting
 - problem solving
 - pacing
 - reframing
 - communication



Jordana Muroff, MSW, PhD,
psychologist & social worker
Start



Symptom Management Skills:

Active Relaxation — Achieving the Relaxation Response

By: Jordana Muroff, Ph.D., MSW



exit the CD

additional resources

listen to mp3
(Progressive Muscle Relaxation)

listen to mp3
(Deep Breathing)

listen to mp3
(Visual Imagery)

Acrobat
PDF File

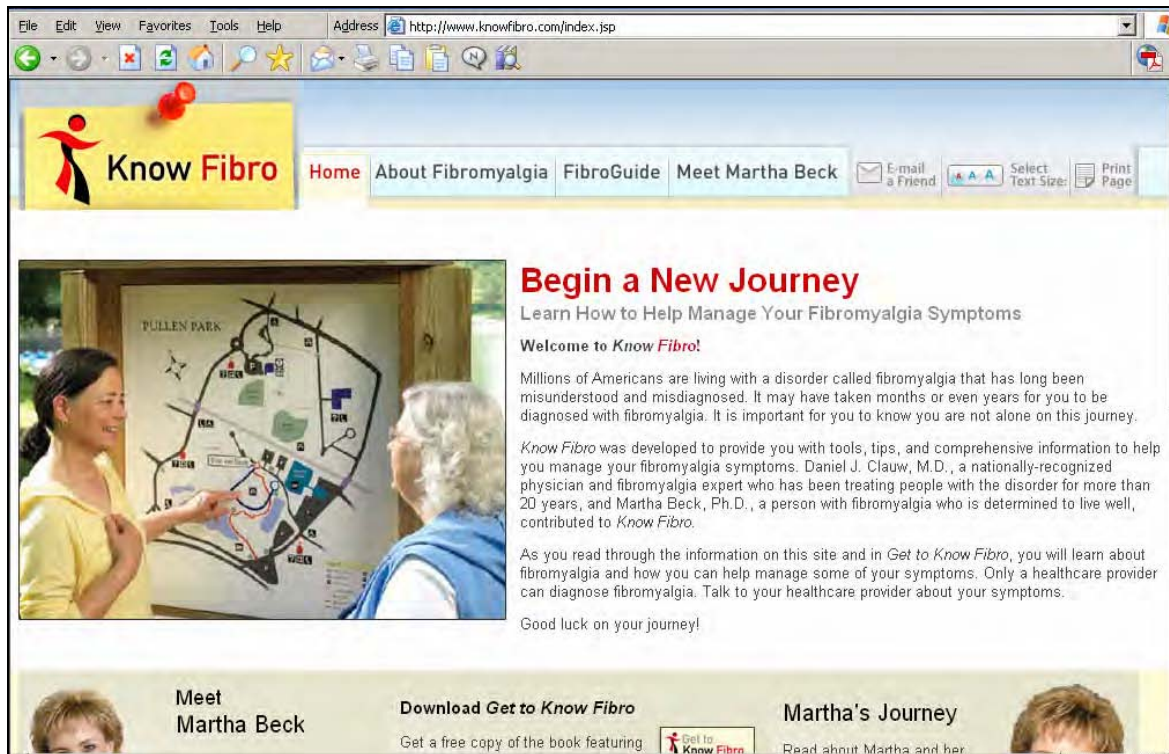
MS Word
worksheet

Screenshots

Know Fibro and Fibro Guide

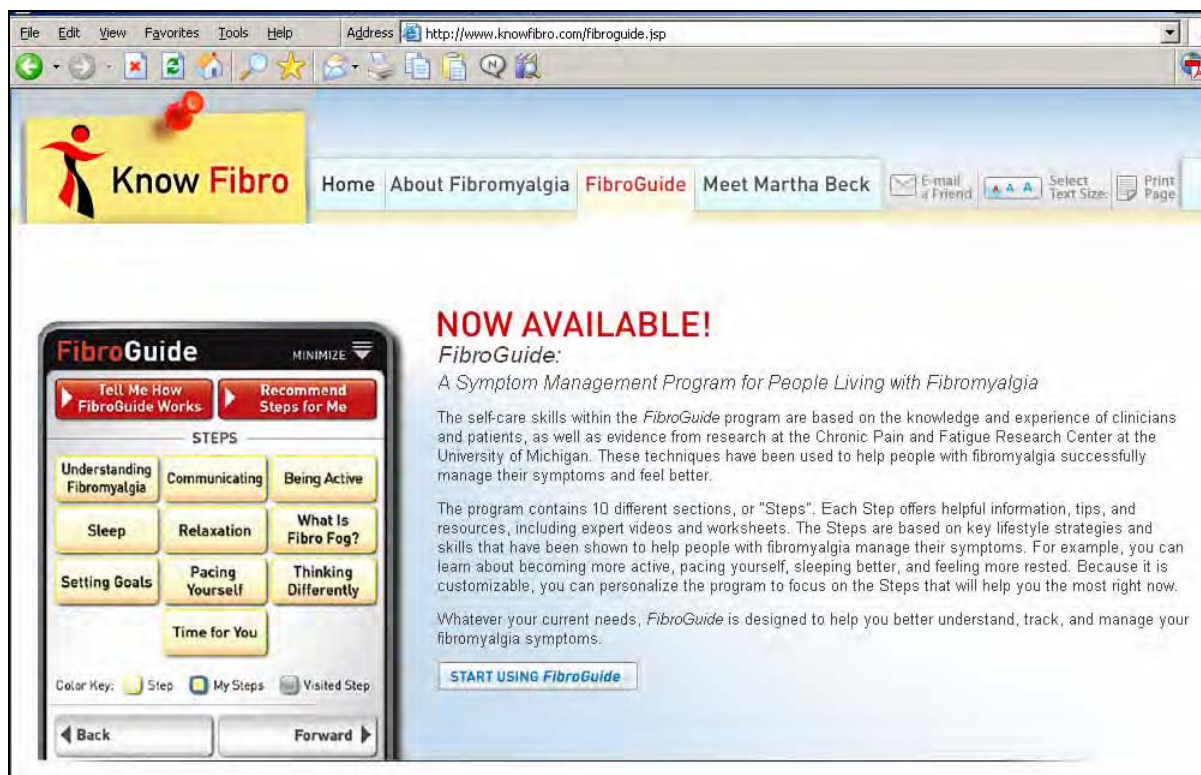
www.knowfibro.com

Introduction to Know Fibro main page:



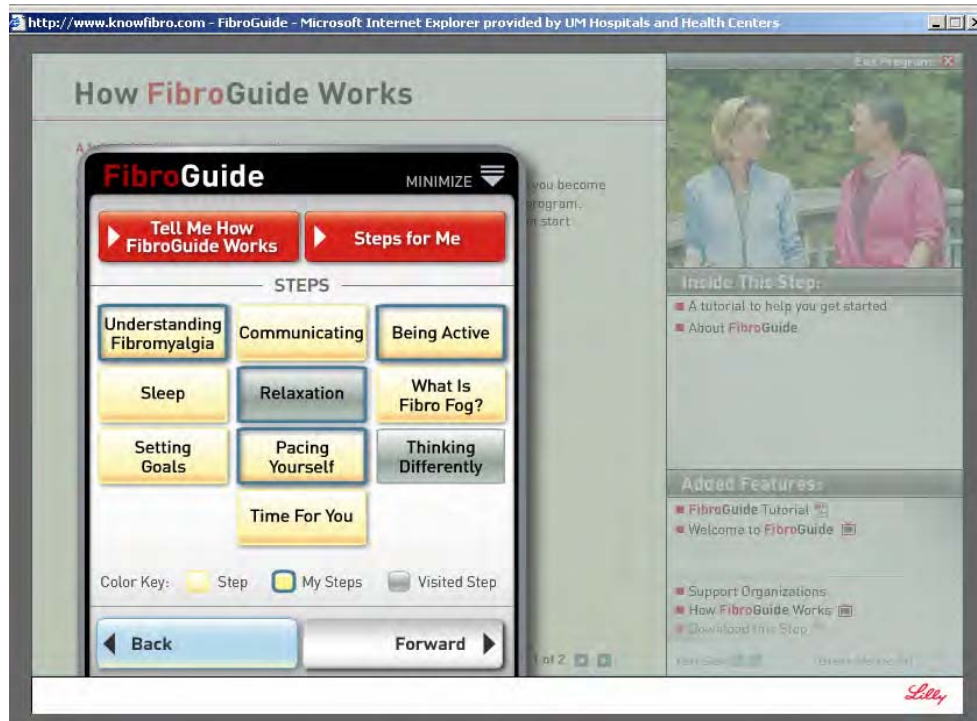
The screenshot shows the Know Fibro main page in a web browser. The address bar displays <http://www.knowfibro.com/index.jsp>. The page features a navigation bar with links: Home, About Fibromyalgia, FibroGuide, and Meet Martha Beck. A yellow banner with a red pushpin icon and the text "Know Fibro" is at the top left. Below the navigation bar, there is a large image of two women looking at a map of Pullen Park. To the right of the image, the heading "Begin a New Journey" is followed by the subheading "Learn How to Help Manage Your Fibromyalgia Symptoms". Below this, a welcome message reads: "Welcome to Know Fibro! Millions of Americans are living with a disorder called fibromyalgia that has long been misunderstood and misdiagnosed. It may have taken months or even years for you to be diagnosed with fibromyalgia. It is important for you to know you are not alone on this journey." The text continues: "Know Fibro was developed to provide you with tools, tips, and comprehensive information to help you manage your fibromyalgia symptoms. Daniel J. Clauw, M.D., a nationally-recognized physician and fibromyalgia expert who has been treating people with the disorder for more than 20 years, and Martha Beck, Ph.D., a person with fibromyalgia who is determined to live well, contributed to Know Fibro." It then states: "As you read through the information on this site and in *Get to Know Fibro*, you will learn about fibromyalgia and how you can help manage some of your symptoms. Only a healthcare provider can diagnose fibromyalgia. Talk to your healthcare provider about your symptoms." The page concludes with "Good luck on your journey!". At the bottom, there are three sections: "Meet Martha Beck" with a small photo, "Download *Get to Know Fibro*" with a link to get a free copy, and "Martha's Journey" with a link to read about her.

Introduction to the Interactive Fibro Guide:

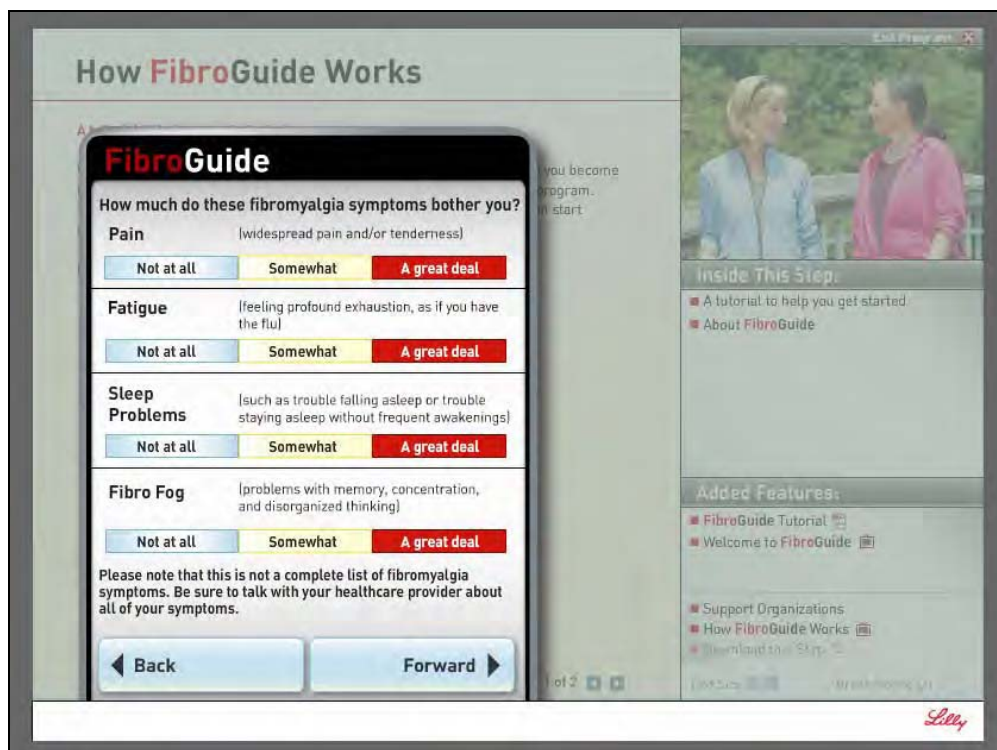


The screenshot shows the Know Fibro Interactive Fibro Guide page in a web browser. The address bar displays <http://www.knowfibro.com/fibroguide.jsp>. The page features a navigation bar with links: Home, About Fibromyalgia, FibroGuide, and Meet Martha Beck. A yellow banner with a red pushpin icon and the text "Know Fibro" is at the top left. Below the navigation bar, there is a large image of a tablet displaying the FibroGuide interface. The tablet screen shows a "FibroGuide" header with a "MINIMIZE" button. Below the header, there are two red buttons: "Tell Me How FibroGuide Works" and "Recommend Steps for Me". Underneath, a "STEPS" section lists various topics: Understanding Fibromyalgia, Communicating, Being Active, Sleep, Relaxation, What Is Fibro Fog?, Setting Goals, Pacing Yourself, Thinking Differently, and Time for You. A "Color Key" at the bottom of the tablet screen indicates: Step (yellow), My Steps (blue), and Visited Step (grey). Navigation buttons "Back" and "Forward" are at the bottom of the tablet. To the right of the tablet image, the heading "NOW AVAILABLE!" is followed by the subheading "FibroGuide: A Symptom Management Program for People Living with Fibromyalgia". The text continues: "The self-care skills within the *FibroGuide* program are based on the knowledge and experience of clinicians and patients, as well as evidence from research at the Chronic Pain and Fatigue Research Center at the University of Michigan. These techniques have been used to help people with fibromyalgia successfully manage their symptoms and feel better." It then states: "The program contains 10 different sections, or 'Steps'. Each Step offers helpful information, tips, and resources, including expert videos and worksheets. The Steps are based on key lifestyle strategies and skills that have been shown to help people with fibromyalgia manage their symptoms. For example, you can learn about becoming more active, pacing yourself, sleeping better, and feeling more rested. Because it is customizable, you can personalize the program to focus on the Steps that will help you the most right now." The page concludes with "Whatever your current needs, *FibroGuide* is designed to help you better understand, track, and manage your fibromyalgia symptoms." A blue button labeled "START USING FibroGuide" is at the bottom.

Customize Fibro Guide for specific symptoms:



Responses identify most applicable virtual modules:



Select modules and adopt suggested strategies:

